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developing

anaesthesia for

Peri-operative Medicine

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PERI-OPERATIVE MEDICINE.

All patients listed for surgery require full preoperative assessment. There are two essential aims of the preoperative assessment. Firstly, the anaesthetist must determine the most appropriate anaesthetic technique dependent on the patient's medical condition, the planned surgery and their own individual preferences. Secondly the anaesthetist must determine the appropriate timing of the anaesthetic/surgery. Surgery may be considered elective, urgent and emergent. Elective should be delayed until the patient is fully optimised. The anaesthetist should not be intimidated into proceeding with anaesthesia if they have doubts. Urgent surgery can be delayed until the anaesthetist has had the opportunity to fully assess and endeavour optimisation. Urgent surgery does not dictate immediate surgery and anaesthesia. There is sufficient time to investigate and correct basic physiological derangements. For example, "emergency appendicectomy" should not proceed without assessment and rehydration. In certain life or limb threatening circumstances it may be necessary to anaesthetise and operate on acutely unwell patients or those with significant medical problems. This should only occur after discussion with the surgical team and the patient. These patients still require full assessment and attempted optimisation concurrent with anaesthesia and surgery.

In general the system of routine preoperative assessment follows reviewing the patient's notes and past anaesthetic charts, obtaining the patient's history including fasting, reflux risk, medication and allergies, patient examination including airway assessment, reviewing investigations, obtaining additional information, explanation and consent, perioperative orders including premedication and documentation of the assessment and perioperative plan.

Some patients will have planned surgery and/or medical disorders that command extra consideration by the anaesthetist during the entire peri-operative period. Specific patient factors may require additional peri-operative investigations, intra-operative and post-operative monitoring, peri-operative medication and altered anaesthetic techniques. For example diabetes presents several specific factors. Long-term diabetic control, peri-operative blood glucose management and end organ dysfunction (cardiac, renal and autonomic nervous system) may each decree particular alterations to routine anaesthetic care.

The essential elements of peri-operative medicine are determining the true urgency of surgery with respect to patient optimisation and identifying specific patient problems that will necessitate additional perioperative anaesthetic strategies beyond routine anaesthetic care.

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MANAGEMENT OF THE ALCOHOLIC PATIENT.

Definition of alcohol use disorders.

Alcohol use disorders range from those with alcohol dependence and abuse to those considered “at risk”. The “at risk” drinker is the person who consumes harmful levels of alcohol but is not alcohol dependent. This amounts to 16 standard drinks per week in men or ten standard drinks per week in women. Harmful drinking is considered by the World Health Organisation to be the level of alcohol use that results in physical or psychological harm, but the patient is not considered to be alcohol dependant.

Alcohol abuse is defined as a maladaptive pattern of use associated with one or more of:

- a failure to fulfil work and social obligations; recurrent use in physically hazardous situations,
- recurrent legal problems (drink-driving for instance) or
- continued use in spite of alcohol related social problems. (1)
-

Alcohol dependence is defined as a maladaptive pattern of use associated with three or more of:

- tolerance;
- withdrawal;
- alcohol taken in larger quantities than intended;
- persistent desire to cut down use;
- time spent obtaining, using or recovering from alcohol;
- social, occupational or recreational tasks being sacrificed and
- continued use despite physical and psychological problems. (1)

Alcohol withdrawal syndrome.

Most people are susceptible to withdrawal symptoms when there is an abrupt cessation of sustained alcohol intake. Withdrawal is not usually seen because most people drink in an episodic rather than a sustained fashion. (2)

Because of the central nervous system depressant effects of alcohol, abrupt cessation of drinking unmasks compensatory overactivity of certain parts of the central nervous system including sympathetic autonomic outflow. (2)

Minor withdrawal occurs after 6 to 36 hours after intake and includes tremor, insomnia, mild anxiety, gastrointestinal upset, headache, diaphoresis and anorexia.

Withdrawal seizures are generalized tonic-clonic convulsions that occur within 48 hours after the last drink. 3 percent of chronic alcoholics have seizures and of these 3 percent develop status

epilepticus. Treatment is controversial and most of these seizures are self-limiting. If the patient develops status epilepticus, short-term phenytoin and benzodiazepines can be used.

Alcoholic hallucinosis is characterized by visual, auditory or tactile hallucinations. They can occur 12-48 hours after cessation of drinking and do not define delirium tremens unless there is a clouding of the sensorium.

Delirium tremens (DTs) will occur in up to 5 percent of those who undergo withdrawal from alcohol. Its onset is usually 48 hours after the last drink and is characterized by hallucinations, disorientation, tachycardia, hypertension, low-grade fever, agitation and diaphoresis. DTs usually lasts one to five days. The risk factors for DTs are a sustained drinking history, previous episodes of DTs, age greater than 30, concurrent illness and more than 48 hours after the last drink.

The DTs will create a catabolic state with increased cardiac output and oxygen consumption. Hyperventilation will decrease pH and reduce cerebral blood flow. The patients are frequently dehydrated and may suffer electrolyte disturbances including hypokalaemia, hypomagnesaemia and hypophosphataemia. Low phosphate may contribute to cardiac failure and rhabdomyolysis.

The stress of surgery may predispose or exacerbate alcohol withdrawal syndrome and this may increase morbidity. (3) The identification of alcohol withdrawal syndrome may be delayed in the peri-operative period. It is therefore important to identify the patient at risk for withdrawal by taking a careful history of alcohol consumption and previous alcohol withdrawal syndromes. These patients will then need to receive prophylaxis.

Prophylaxis for alcohol withdrawal will need to begin upon cessation of drinking. It should not be delayed until after surgery, because it is possible to develop the withdrawal syndrome intra-operatively. This will compound any surgical stress response and contribute to a worse outcome.

The first line drug for prophylaxis is a benzodiazepine. The use of diazepam is favoured because it has a long half-life and active metabolites. In the patients with advanced cirrhosis, an agent with a shorter half-life such as oxazepam may be more prudent. Diazepam is given in doses of 5 to 10 mg intravenously every five minutes until the patient is calm but awake. Thereafter, a symptom-triggered approach can be used. This involves the administration of benzodiazepine based on the patient's clinical condition after initial loading with diazepam.

Refractory delirium tremens can be treated with phenobarbitone in addition to diazepam, or with propofol.

Alcohol should not be used in the patient with acute withdrawal. Phenothiazines and butyrophenones lower the seizure threshold and are not recommended. (2)

Short and long term effects of alcohol use.

Nervous system.

Acute intoxication depresses the central nervous system, which will lead to blunting and loss of motor, sensory and cognitive function. There also depression of inhibitory pathways leading to behavioural disinhibition.

Chronic alcohol use is associated with peripheral and central nervous system effect. Peripheral neuropathy can lead to “stocking” distribution of sensory effects and there can be proximal myopathy leading to weakness and muscle wasting. Long-term use of ethanol is associated with a higher incidence of dementia.

Psychosis is related to nutritional deficiencies, primarily of B1 (Thiamine). Wernicke’s encephalopathy is an acute disorder that consists of ocular-motor disorders, ataxia and an altered mental state. Korsakoff’s psychosis consists of amnesia (both retrograde and anterograde), disorientation and confabulation. Metabolic stress in conjunction with a glucose load typically triggers Wernicke-Korsakoff’s syndrome so it is recommended that these patients receive thiamine before receiving glucose. (4)

The other long-term effects of alcohol abuse relate to withdrawal syndromes, which have already been discussed.

Cardiovascular system.

Long-term alcohol use will cause a gradual increase in blood pressure.

Atrial fibrillation can occur in association with acute binge drinking as well as with chronic alcohol abuse. There is a 34% increased risk of developing atrial fibrillation in the chronic alcoholic. (4)

A dilated left ventricle and a small reduction in ejection fraction characterize alcoholic cardiomyopathy. There is a rise in pulmonary pressures, right heart failure and arrhythmias. Thiamine deficiency will cause wet beriberi or high output cardiac failure. The high cardiac output is thought to be due to systemic vasodilatation and increased venous return.

The patient who is withdrawing from alcohol has heightened sympathetic nervous system outflow which can trigger heart failure.

Respiratory system.

Because of immunosuppression, the alcoholic patient is at increased risk for atypical bacterial pneumonia (such as the gram negative, *Klebsiella pneumoniae*). Aspiration pneumonia can also occur due to a depression of protective reflexes with intoxication.

Gastrointestinal and Hepatobiliary system.

Gastric pathology is more common with alcohol use. Acute gastritis, oesophagitis and pancreatitis can occur with binge drinking. Chronic use increases gastric acid reflux.

Alcoholic liver disease occurs in three major forms, which commonly overlap. They are fatty liver, alcoholic hepatitis and cirrhosis. The risk factors for the development of severe alcoholic liver disease are the ingestion of over 5-7 standard drinks per day (12g of alcohol per standard drink) for 10 years in men and over 2-4 drinks per day in women.

Fatty liver is the most common response to toxins. Fatty liver is most commonly asymptomatic but it may present with right upper quadrant pain, hepatomegaly, nausea and jaundice. It will occur in over 90% of binge and chronic drinkers and is potentially reversible with the cessation of drinking. Laboratory investigations usually show moderately elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT), high cholesterol and triglycerides. (5)

Alcoholic hepatitis is characterised by hepatocyte injury and is thought to be a precursor to cirrhosis. It may be potentially reversible with the cessation of drinking, whereas cirrhosis is not.

Fortunately only 15% of alcoholics develop alcoholic liver disease. The main features of hepatitis are fever, jaundice and abdominal pain. Some patients are asymptomatic. The AST and ALT are markedly elevated (2 to 7 times normal) and high bilirubin is common. Coagulopathy, anaemia and low albumin indicate severe disease. If the patient becomes critically ill with ascites, variceal haemorrhage, encephalopathy or hepatorenal syndrome, then the prognosis is poor with a mortality of 70%. Treatment is mostly supportive, but glucocorticoids have been used. Abstinence from alcohol is important for those with potentially reversible disease. (5)

Preoperative assessment of the patient with alcohol abuse.

Preoperative assessment involves the diagnosis of an alcohol use disorder with careful questioning, the detection of end organ damage and the assessment of the potential for alcohol withdrawal syndrome. Baseline investigations include, electrocardiography (ECG), electrolytes (hypokalemia, hypomagnesaemia, hypophosphatemia, hypoglycaemia), full blood count (anaemia, low platelets), coagulation (elevated prothrombin time), and liver function testing where hepatitis is suspected.

Where there is a potential for withdrawal syndrome, diazepam should be administered according to symptoms.

If there is enough time, the patient should abstain from alcohol pre operatively. This may involve referral for counselling and a program of detoxification. A study from Denmark involving 32 patients for colorectal surgery with an alcohol consumption of at least 60g per day, showed that one month of abstinence reduced postoperative morbidity (31% versus 74% $P=0.02$) compared to continuous drinkers. The most common complications were infection, cardiopulmonary insufficiency and bleeding. The mechanism is probably a reduction in organ dysfunction and a reduction of the exaggerated response to surgical stress. (6)

Chronic alcohol abusers should receive multivitamins and high dose thiamine (100mg) to prevent stress-induced Wernicke-Korsakoff syndrome.

The acutely intoxicated patient.

The acutely intoxicated patient is more sensitive to the effects of barbiturates, benzodiazepines and opioids. There is generally a lesser anaesthetic requirement. The intoxicated patients can be assumed to have an increased risk for pulmonary aspiration and therefore will require a rapid sequence induction after premedication with a non-particulate antacid such as sodium citrate and ranitidine. In addition, the intoxicated patient will have an inability to withstand acute blood loss and a decreased brain tolerance to hypoxia.

Alcohol interferes with platelet function and increases the concentration of plasma catecholamines. (7)

If the procedure is elective, it is best to postpone the operation until the patient is sober so that adequate fasting is achieved and there is less interaction with anaesthetic medication. There is a tendency to hypoglycaemia in the intoxicated patient, so blood glucose should be monitored. In an emergency, precautions to prevent aspiration will need to be taken and invasive blood pressure and central venous pressure monitoring may be required where significant blood loss is expected.

The sober chronic alcoholic.

After careful pre operative assessment, as outlined previously, routine monitoring should be established (blood pressure, ECG, pulse oximetry, end tidal carbon dioxide and agent monitoring) and invasive monitoring may be required depending on the presence of end organ damage and the surgical procedure.

Due to increased resistance through the portal vein, patients with liver disease rely on hepatic arterial flow for perfusion and are at risk for hepatic ischaemia if there is hypotension, an arterial line may be required.

The assessment of volume status is improved in the presence of an in dwelling urinary catheter and central venous pressure catheter. Those with severe cardiac disease may require a pulmonary artery catheter to monitor filling pressures and cardiac output.

In the sober patient, there is less risk for aspiration compared to the intoxicated patient unless there is reflux oesophagitis or raised intra abdominal pressure due to ascites. It is important to realize that the presence of oesophageal varices may preclude the use of oro- or nasogastric tubes.

There is no evidence that one anaesthetic technique is better than any other but it needs to be remembered that coagulopathy and platelet dysfunction will be a contraindication to spinal or epidural anaesthesia due to the risk of spinal haematoma. The cardiac depressant effects of the volatile agents may be exaggerated in the presence of cardiomyopathy.

There have been several studies to show that there is an increased requirement for anaesthesia and analgesia in the patient with chronic alcohol use. (8) (9) This increase in anaesthesia and analgesia requirements is thought to be due to cross-tolerance with alcohol but it may be a pharmacokinetic phenomenon. In the study assessing the dose of propofol required for loss of consciousness in the chronic alcoholism, 26 chronic alcoholics and 20 non-habitual drinkers were studied. The dose for loss of consciousness in the alcoholic group was 4.2 mg per kg compared to 2.2 mg per kg in the control group ($P < 0.001$). The blood concentration at loss of consciousness between these groups was not significant. (8). The dose requirement of thiopentone has not been shown to be increased. (7)

Muscle relaxants that require organ based (liver or renal) metabolism and excretion should be avoided. Suxamethonium may have a slightly prolonged duration of action if there is liver dysfunction and reduction in plasma cholinesterase. There is a larger volume of distribution in the presence of liver cirrhosis, which may necessitate larger initial doses of non-depolarising muscle

relaxants. Atracurium is a good choice for muscle relaxation in the patient who does not require a rapid sequence induction because it is not metabolised in the liver.

The surgical stress response is enhanced in the alcoholic patient. This may increase postoperative morbidity due to increased cardiovascular demand and immunosuppression. In addition, it is difficult to distinguish between the stress response and alcohol withdrawal syndrome under anaesthesia. The two may occur simultaneously producing additive effects

Post operative care.

Alcoholic patients show a two to five fold higher rate of postoperative complications so deserve special postoperative attention. There is a two-fold increase in bleeding complications after surgery and immune suppression results in higher rates of infection (wound, chest and urinary infection). (10)

Opioid analgesic requirements may be increased in the alcoholic patient, so the use of adjuvants for analgesia is attractive, however, the patient with liver disease is more susceptible to overdose and hepatic necrosis when taking paracetamol and non-steroidal drugs will further impair platelet function.

Withdrawal occurs after alcohol intake ceases and symptoms should be sought post operatively given that severe alcohol withdrawal syndrome symptoms typically peak within four days.

Conclusion.

Alcohol use disorder is common among surgical patients. The prevalence is about 20%. The alcoholic patient is at risk for major postoperative morbidity including prolonged intensive care and hospital stay, respiratory and cardiovascular complications, infection and surgical bleeding. Of significant concern, is the risk of alcohol withdrawal syndrome, which carries significant mortality.

The challenge for the anaesthetist is to identify the patient who has alcohol use disorder, detect any end organ damage and assess for the risk of withdrawal. Ideally, the patient will be seen some time prior to surgery to enable a referral to an addiction specialist and undergo a period of abstinence. This is not always practical, and indeed it may be necessary to anaesthetise an intoxicated patient who has suffered trauma.

Preoperative assessment will need to include a detailed history and examination, looking for the multiple complications of chronic alcohol use including hepatic, pulmonary, cardiac and neurological complications. Investigation will need to include a search for metabolic and electrolyte abnormality, coagulopathy and anaemia and an ECG to detect cardiac arrhythmias.

There is no anaesthetic technique that is ideal for the chronic drinker, but the anaesthetist should bear in mind the risk of aspiration, the change in sensitivity to anaesthetic medications and the risk of coagulopathy.

Postoperatively, the patient will need to be carefully monitored. Ideally this will be in a high dependency area where he can be observed for signs of withdrawal and cardiac, respiratory and infectious complications.

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SMOKING AND ANAESTHESIA.

Smoking is a major health risk. Nearly 20% of all deaths in developed countries can be attributed to tobacco use. Its deleterious effects are well known. Apart from being a risk factor for several diseases, it produces acute physiologic disturbances, which have implications for anaesthesia.

Tobacco smoke contains many toxins, the most important ones being nicotine and carbon monoxide. Nicotine is a central nervous system stimulant and has a sympathomimetic effect that causes an increase in heart rate that lasts 20-30 minutes. It will also increase blood pressure and cause peripheral vasoconstriction, which will improve after 12-24 hours of abstinence.

Carbon monoxide in cigarette smoke binds to haemoglobin and reduces its oxygen carrying capacity. It may also have negative inotropic and arrhythmic effects. The elimination half time of carbon monoxide is short at four to six hours, so that by 12 or 18 hours, the levels of carboxyhaemoglobin have dropped from 6.5 to 1.1% and the p50 of haemoglobin has increased from 22.9 mmHg to 26.4 mmHg (1). The increased concentration of carboxyhaemoglobin will cause the pulse oximeter to overestimate the saturation of oxygen.

Smoking is a risk factor for several diseases including many cancers, coronary artery and peripheral vascular disease, and respiratory disease. The degree of vascular and pulmonary damage caused by smoking is related to the duration of smoking. Typically, the amount of cigarette smoke a person has been exposed to is expressed in the number of pack-years he or she has smoked.

Physiological effects.

Cardiovascular effects.

Smoking increases myocardial work and impairs oxygen delivery as well as promoting atherosclerosis. It contributes to exercise induced angina and arrhythmias in those with coronary artery disease. Abstinence over several months will reduce the risk for all cause mortality in those smokers with cardiovascular disease by one third. (18)

The cardiovascular response to induction and intubation is exaggerated in smokers. (5) In a study of 40 subjects, Malhohra et al showed that there was a more prominent response to induction and intubation in smokers than in non-smokers. There was a greater increase in heart rate, blood pressure and a three-fold increase in the incidence of arrhythmias. (12)

Respiratory effects.

Chronic smoking will cause an increase in hematocrit and will increase blood viscosity. This polycythemia will take a few days to reverse after cessation of smoking.

In the lungs, there is an increase in mucous production secondary to mucous gland proliferation, impairment of macrophage function (with aggregation and reduced phagocytic and microbicidal

activity) (24), impaired ciliary function, a reduction in surfactant integrity, which causes airway closure, and an acceleration of the age-related reduction in forced expiratory volume in one second (FEV1).

Smoking is related to an increase in peri operative pulmonary complications. Warner et al (25) collected retrospective data about smoking history and made prospective observations about pulmonary complications in 200 patients who underwent coronary artery bypass grafting and found that those who ceased smoking for eight weeks or more had a 60% reduction in postoperative pulmonary complications compared to those who continued to smoke. The complications studied were the presence of purulent sputum, fever, need for respiratory care, bronchospasm, pleural effusion, segmental pulmonary collapse and pneumonia. In the same study, the investigators found that those smokers who had quit for less than eight weeks had an increase in pulmonary complications compared to those who continued to smoke. (57% for recent quitters compared to 33% in those who continued to smoke.) This has not been borne out in more recent studies.

Airway reactivity is exaggerated in smokers compared with non-smokers. There is an increase in upper airway response to chemical stimuli, which returns to normal over 48 hours to ten days. (2) The rate of adverse events such as cough, breath holding and laryngospasm on induction is higher in active as well as passive smokers compared with non-smokers. (3) (14)

Effects on wound healing.

Immune function is impaired by cigarette smoking as is wound healing and there is an increase in the rate of postoperative wound breakdown and infection. In 2002, Moller *et al* studied 120 patients undergoing hip and knee arthroplasty. There were sixty patients in each group, one control group of smokers and another group that underwent intervention to stop smoking six to eight weeks before surgery. The overall complication rate was 18% in the intervention group, and 52% in the control group ($p=0.003$). The rate of wound complications was 5% in the intervention group and 31% in the control group ($p=0.001$) and the rate of cardiovascular complications was 0 versus 10% (although this did not reach statistical significance). The authors concluded that smoking was the single most important risk factor for the development of postoperative complications; especially wound healing, cardiac and pulmonary complications and the need for post operative intensive care in patients undergoing elective hip or knee arthroplasty. (19)

Smoking is a risk factor for non-union of spinal fusions and is also a risk factor for osteoporosis. (18)

In 2003, Manassa (10) et al looked at wound healing problems in smokers and non-smokers after 132 abdominoplasties and found that the rate of wound problems and dehiscence was higher in smokers (47.9%) compared with non smokers (14.8%) ($P=0.01$).

Smokers undergoing ambulatory surgery have also been found to be at higher risk for wound complications (as defined by purulent discharge, redness and serous discharge with positive microbial cultures requiring antibiotics) than non-smokers. (3.6% compared with 0.6% in non-smokers in a study of 489 adults undergoing ambulatory surgery $p=0.019$) (14).

The possible mechanisms of poor wound healing include an effect on fibroblasts and immune cells important to healing via the action of nicotine on their nicotinic acetylcholine receptors; microvascular disease in smokers; and modulation of the neurogenic component of the inflammatory response to injury via effects on the sympathetic nervous system. (18)

Central nervous system effects.

Analgesic requirements are increased; the mechanism of which is not fully clear, but may be due to enzyme induction or withdrawal of endogenous opioid stimulation. Neuronal nicotinic acetylcholine receptors modulate pain, which may contribute to this effect. This effect on analgesic requirements is improved after 6-8 weeks of abstinence. (9) Smoking is also a risk factor for some painful conditions such as back pain. (18)

Nicotine is addictive. It acts via the activation of dopaminergic neurons in the ventral tegmental area. Exposure to nicotine can induce feelings of reward and prolonged exposure can induce long lasting plastic changes in the central nervous system and abstinence will commonly result in a withdrawal syndrome. (18)

Since most hospitals are now smoke-free, a period of peri operative abstinence will occur in the surgical patients. Warner et al (23) studied perceived psychological stress in smokers undergoing elective surgery and found that pre operatively, smokers reported increased baseline stress but that smoking did not affect changes in stress over the peri operative period. Withdrawal scores and higher craving was present in heavy smokers but their craving actually decreased post operatively, a finding confirmed by others. Withdrawal symptoms may be mitigated under stressful conditions that demand forced abstinence. This may present an opportunity to support the patient to quit smoking permanently. (23).

Anaesthetic drugs and smoking.

In 2004, Wild et al revealed that smokers inhaling isoflurane had a 45% incidence of adverse airway events compared to 10% in those inhaling sevoflurane ($p=0.013$). The adverse airway events included cough, breath holding and mild laryngospasm. (15).

Relaxants.

There is a greater sensitivity to atracurium in smokers and the dose requirements for vecuronium are increased by 25% in smokers. (4)

Smoking does not alter the dose requirements and pharmacodynamics of rocuronium. (8)

Opioids.

Morphine and pethidine metabolism is increased which may partly explain why there is an increase in analgesic requirements in the smokers, and why postoperative nausea and vomiting is reduced.

Thiopentone and benzodiazepines.

Cigarette smoking does not affect thiopentone pharmacodynamic and pharmacokinetic behaviour but those receiving benzodiazepines appear to be more resistant to their sedative effects than non-smokers. (7)

Post operative nausea and vomiting (PONV).

PONV is reduced in smokers. The cause is unclear but it is postulated that this may be due to an adaptive response to a repeated emetic stimulus. (6). Alternatively, the reason may lie in altered drug handling in the body by smokers. The polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke induce the liver enzyme CYP1A2 activity three-fold. This enzyme is a major enzyme involved in the metabolism of drugs, including diazepam. The metabolism of morphine and pethidine is also increased and these are well known for producing emesis. The volatile anaesthetics are metabolised by the liver enzyme CYP2E1, which is induced by nicotine and PAHs. Because volatiles are a major cause of PONV, this may also explain some of the reduction in PONV. (6)

The reduction in PONV in smokers is not related to preoperative carbon monoxide levels, which reflect how recent the last cigarette was. (11)

Perioperative abstinence.

Peri operative abstinence from cigarette smoking should be encouraged. Cessation of smoking for 48 hours will reduce carboxyhemoglobin levels and allow the oxyhaemoglobin dissociation curve to shift back towards the right so as to increase tissue availability of oxygen.

Upper airway sensitivity to chemical irritants returns to normal within a few days of quitting.

Four to six weeks of abstinence reduces postoperative pulmonary complications, returns the immune responses to normal, and normalizes hepatic enzyme function. (Smoking induces hepatic enzymes.) Four weeks of abstinence seems to improve wound healing. (16)

In spite of the earlier findings by Warner (25), a beneficial effect has been observed from even a short period of preoperative abstinence (less than six weeks). Longer periods of cessation seem to be more effective in reducing the incidence or risk of postoperative complications but there was no increased risk in the postoperative complication rate from short-term cessation. An optimal period of cessation cannot be determined from available evidence. (22).

Two to three months of abstinence will improve ciliary function, pulmonary mechanics and reduce sputum production. Small airways function improves after one month and will continue to improve for 12 months after abstinence. (9)

Six months is required for immune function to return to normal. That is, normal immunoglobulin, cytokine and macrophage levels. (9)

Surgeons and anaesthetists should advise their patients to stop smoking preoperatively and encourage ongoing abstinence. There is evidence that a physician's advice to quit smoking increases abstinence rates. (13) In a survey of anaesthetists and surgeons to examine practices and attitudes about cigarette smoking intervention in the peri operative period by Warner et al, 90% of surgeons and anaesthetist reported almost always asking about smoking history, yet only 30% of anaesthetists and 58% of surgeons almost always advised their patients to quit. Warner also found that only 40% of survey respondents knew that nicotine patches are readily available without a prescription and 35% agreed that nicotine replacement therapy (NRT) was safe to use after surgery. Less encouraging was the finding by Myles et al (14) that despite receiving advice to stop smoking in the pre operative period, only 3% of smokers recalled receiving such advice.

NRT is a valuable tool, which increases the chance of quitting. It provides a steady dose of nicotine via the transdermal route to reduce the craving produced by abstinence from cigarettes. The effects of transdermal nicotine have been studied and found to be free of significant adverse effects in healthy volunteers. (20) There is evidence that NRT is safe even in patients with cardiovascular disease. (18) Other components of cigarette smoke besides nicotine contribute to adverse effects and the peak serum concentration with NRT is lower than that produced by cigarettes.

Transdermal nicotine has been found to increase heart rate after endotracheal intubation. In a study performed on 60 healthy smokers the response to intubation was measured in those wearing nicotine and those wearing placebo patches and it was found that the increase in heart rate was greater in those wearing the nicotine patches. (21). In light of this, caution should be exercised in those patients at risk of cardiovascular disease who may not tolerate such a rise in heart rate on induction.

NRT probably does not increase wound infection rates but there is little evidence to support or refute this.

Conclusion.

In summary, cigarette smoking is detrimental to health. In the surgical patient, the presence of cardiovascular and respiratory disease needs to be considered. Nicotine and carbon monoxide have important but short-term effects on the cardiovascular and respiratory system, which will reduce oxygen delivery to the tissues and put the patient at risk for peri operative ischaemia. Postoperative wound infection and respiratory complication rates are increased and analgesic requirements are increased. The peri operative period may present an opportunity to encourage smokers to quit and nicotine replacement therapy may assist the patient to do so.

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ANAESTHESIA FOR THE DIABETIC PATIENT.

Epidemiology.

It is estimated that 2.4% of the U.S. population are diabetic and a further 3.2% have glucose intolerance. (1) In 2003, 194 million people aged 20 to 79 years (or one in 20 adults) had diabetes. Three quarters of them were from the developing world. (2) Almost one million people die because of diabetes each year and it is estimated that diabetes shortens life expectancy by up to 15 years.

Classification of diabetes and diagnostic criteria for diagnosis

The World Health Organization has recommended that the classification of diabetes should be by underlying cause rather than by age of onset or the requirement for insulin. The new classification is: type one diabetes, which is characterised by insulin deficiency and type two diabetes, which is characterised by peripheral insulin resistance and is often associated with a failure to secrete insulin.

The diagnosis is made on a random plasma glucose level of greater than 11.1 mmol/L (>10 mmol/L blood glucose) or fasting plasma glucose greater than 7.0 mmol/L (6.1 mmol/L). If fasting plasma glucose concentrations are between 6.1 mmol/L and 7.0 mmol/L (5.6-6.1 mmol/L blood glucose), then this represents impaired fasting glycaemia.

Gestational diabetes is glucose intolerance, which presents during pregnancy.

Prevention of diabetes.

The two strategies that are currently used to try to delay or reduce the onset of diabetes are lifestyle interventions and drugs. Lifestyle interventions are labour intensive but may be effective in reducing the incidence of diabetes by 58% (3). The interventions focus on weight reduction and exercise.

Metformin showed a reduction in the incidence of diabetes of 31% over 2.8 years (3) and in people with obesity, orlistat has been shown to reduce the risk by 37% when compared with placebo. (3)

The key cost-effective interventions for the prevention and treatment of complications are: moderate glycaemic control with insulin, oral hypoglycaemics, diet and exercise which will reduce microvascular disease; blood pressure control which will reduce macro and microvascular disease and foot care which will reduce foot disease and amputations. These three interventions are cost saving and highly feasible. (2).

Drug therapy.

The mainstay of diabetic therapy is to achieve normo glycaemia, as many of the acute and chronic complications of diabetes related to the presence of hyperglycaemia and impairment of carbohydrate metabolism.

In the type one diabetic there is a lack of insulin secretion due to a destruction of pancreatic beta cells so making the patient prone to lipolysis, proteolysis and ketogenesis. These are prevented in the presence of minimal insulin. Insulin therapy is required for the type one diabetic.

Insulin may be extracted from beef or pork pancreas or synthesised using recombinant DNA technology from *E. coli*. The three types of insulin are the fast acting, intermediate acting and long acting. The soluble insulins have a rapid onset and short duration of action, administered intravenously, they have a half-life of five minutes and subcutaneous injection result in a peak concentration at 2-4 hours and a duration of 30 minutes to 8 hours. The intermediate acting insulins have an onset of 2-4 hours with peak concentrations occurring at 6-12 hours and a duration of over 18 hours. The long acting insulins are suspended with either protamine or zinc (or both) and have an onset time of 4-8 hours with a peak at 14-24 hours and duration of up to 36 hours. Frequently mixtures of different types of insulin are used in order to achieve a rapid onset and long duration of action.

Type two diabetics make up 90% of the diabetic patients. The type two diabetic patients have insulin resistance. There is usually some ability to secrete endogenous insulin but there is peripheral insulin resistance in the tissues, which results in hyperglycaemia. Type two diabetics are frequently managed with diet-control and oral hypoglycaemics initially but may ultimately require exogenous insulin therapy.

Oral hypoglycaemics are grouped into the sulphonylureas (such as glibenclamide and glicazide), the biguanides (metformin), the thiazolidinediones and modifiers of glucose absorption from the gut. (4)

The sulphonylureas include tolbutamide, chlorpropamide, glipizide and glimepiride. They increase the release of endogenous insulin and increase the sensitivity of tissues to the peripheral actions of insulin. These drugs typically have a duration of action of up to 24 hours, except chlorpropamide which has a duration of action of up to 72 hours.

The biguanides decrease hepatic glucose output and increase insulin action. The only drug in use from this group is metformin, which has an association with the development of lactic acidosis.

Thiazolidinediones such as rosiglitazone and pioglitazone increase peripheral glucose uptake and decrease gluconeogenesis. These drugs may cause hepato-toxicity.

The alpha-glucosidase inhibitor, acarbose, suppresses the breakdown of carbohydrates in the gut to delay the rise in post-prandial blood glucose.

Good glycaemic control in the diabetic has been found to reduce the development and progression of microvascular complications such as retinopathy, nephropathy and neuropathy, but a reduction in macro vascular complications has not been confirmed. (5)

Pre-operative assessment.

The pre-operative evaluation of the diabetic surgical patient should include a determination of the type of diabetes, the current drug management and adequacy of control, a search for the complications of diabetes and the formulation of a plan to manage peri operative glucose concentrations.

Control of blood sugar

In the elective surgical patient, there is often time to evaluate the adequacy of glycaemic control. The patient may keep a record of their blood sugar levels, or a glycosylated haemoglobin concentration can be measured to determine how well the blood sugar has been controlled in the previous few weeks. If the HBA1c is greater than 9%, a referral to an endocrinologist is indicated, as this suggests that glycaemic control is poor and microvascular complications are more likely.

An evaluation of other risk factors for cardiovascular disease should be made including hypertension, smoking and high cholesterol as the most common cause of peri operative morbidity in the diabetic is ischaemic heart disease. (1)

Complications

The most serious acute complications of diabetes are those related to metabolic disturbance. That is, ketoacidosis and hyper osmolar non-ketotic coma. Acute hyperglycaemia leads to osmotic diuresis, weight loss and thirst. Hypoglycaemia is more common in the type one diabetic patient and may present as coma.

Ketoacidosis is a life-threatening complication with mortality of 5-10%. The precipitating event may be an infection, surgical stress, trauma or lack of insulin. Sometimes it is the first presentation of type one diabetes. The key features are hyperglycaemia, dehydration, hyperosmolarity and the production of ketones with acidosis. Treatment consists of rehydration, administration of insulin and correction of electrolyte disturbance.

Non-ketotic hyper osmolar state occurs more commonly in the type two diabetics and is precipitated by stress, infection or other illness. The key features are severe dehydration, hyperglycaemia and hyperosmolarity. Confusion and coma can be present and thrombotic events can complicate the picture. Treatment consists of rehydration and a gradual correction of blood sugar over 24 hours. Frequent neurologic monitoring is recommended due to the risk of cerebral oedema. (5)

The chronic complications of diabetes relevant to the anaesthetist include atherosclerosis, cardiomyopathy, microangiopathy (resulting in renal disease), neuropathy (including autonomic neuropathy), stiff joint syndrome and the reduction in wound healing with increased risk of infection.

Atherosclerosis is more common in the diabetic than in the non-diabetic patients, and the outcome of a coronary event is worse. Silent ischaemia is more common in due to the presence of autonomic neuropathy and other cardiac risk factors. If the diabetic patient has been assessed to be

at increased risk of cardiovascular disease, there is no contraindication to the administration of perioperative beta-blockers. The selective screening of patients with multiple risk factors for cardiac disease has been discouraged because there is no evidence to support intervention (revascularization) in the asymptomatic diabetic patients. (4) However, the asymptomatic type one diabetics with severe nephropathy for renal transplantation have been shown to benefit from screening and revascularization. Similarly it may be appropriate for the high risk diabetic (especially those with metabolic syndrome) that are to undergo major elective non cardiac surgery to be screened and revascularized. (4)

The patients with poor glycaemic control have a higher incidence of microvascular disease, which includes retinopathy, and renal disease. Micro albuminuria may precede overt renal disease and some of these patients may have been commenced on an angiotensin converting enzyme inhibitor to slow the progression of renal disease. No particular agent has been shown to be reno-protective in the peri operative period and the best strategy to protect the kidneys remains the provision of adequate renal perfusion with hydration and support of an adequate blood pressure. (4) It would be prudent to avoid the use of potentially nephrotoxic drugs in these patients, and to use caution when administering drugs that are renally cleared.

Autonomic neuropathy is detectable in up to 40% of type one and 17% of type two diabetic patients, with only a small proportion being symptomatic. The symptoms include gastroparesis, postural hypotension, diabetic diarrhoea and bladder paresis. (4) The gastroparesis increases the risk of regurgitation and aspiration, which may be reduced with the use of metoclopramide.

The use of prokinetic agents to empty the stomach had been advocated to help reduce the risk of pulmonary aspiration in the diabetic patient. Their use should be limited to the poorly controlled diabetic with elevated HbA1c levels, as it has been demonstrated that 8 hours of fasting will result in most patients without evidence of gastroparesis. (6)

Autonomic neuropathy may impair the ability to mount a compensatory cardiovascular response to hypotension and lead to intraoperative haemodynamic instability. (5)

Peripheral neuropathy is common. The prevalence of peripheral neuropathy increases with the duration of diabetes and severity of hyperglycaemia. (7). Neuropathy may also occur in the patient with impaired glucose tolerance. Clinically, it affects unmyelinated C or small myelinated fibres (A delta), with sensory symptoms, pain and autonomic dysfunction. (7) Diabetic neuropathy is commonly associated with pain, which may be quite debilitating. The pain is thought to be caused by damage to small fibres. (7) The best treatment to avoid neuropathy is intensive glycaemic control. In those with mild pain, tricyclic antidepressants and anticonvulsants may help. In moderate or severe pain, methadone has been suggested because of its NMDA antagonist effects, and inhibition of noradrenaline and serotonin reuptake. (7) The diabetic patient who is being considered for regional anaesthesia should have his or her pre-existing neurologic deficits noted before the block is performed. Careful patient positioning is important to avoid pressure areas during anaesthesia.

Chronic hyperglycaemia will cause glycosylation of tissues, including joints. Difficult intubation may occur more frequently in the diabetic patient. One way of assessing this is to use the prayer

sign. Patients who are unable to appose their interphalangeal joints with their palms together are considered to be at risk of difficult intubation.

Perioperative management.

The surgical stress response and diabetes

The stress response to surgery is characterized by an elevation of catecholamines, growth hormone, glucagon and cortisol and a depression of insulin levels. This leads to glycogenolysis and gluconeogenesis and ultimately in a rise in blood sugar levels.

Hyperglycaemia increases wound infection and affects wound healing and will worsen the outcome after neurologic damage and myocardial ischaemia.

Protein and glucose catabolism occurs in response to major surgery and the catabolic response is exaggerated in the diabetic patient. When carbohydrates have been administered preoperatively, postoperative insulin resistance and protein losses are reduced. (6)

Minimally invasive surgery, epidural analgesia and insulin infusions have been proposed to reduce perioperative insulin resistance and elevated blood sugar levels. (6).

Peri operative Risks and their management

There is a significant risk of myocardial ischaemia, stroke and renal insufficiency in the diabetic patient. Intraoperative hypothermia is more common in the diabetic due to neuropathy, as is respiratory arrest.

Beta-blockers

The use of beta blockers has been advocated to reduce perioperative myocardial events in diabetic patients. A study published in 2005 which assessed the effect of peri operative beta blockade on hospital mortality after major non cardiac surgery in over 650, 000 patients demonstrated that peri operative beta blocker therapy resulted in a significant reduction of in-hospital mortality amongst high-risk, but not low-risk patients. (6) (11)

Statin therapy

The use of statins pre operatively may reduce the risk for cardiovascular events. There is one prospective randomised trial that examined the effects of short-term statin therapy during the perioperative period that showed a reduction in the incidence of cardiovascular events in the first 6 months after surgery. Atorvastatin was administered to patients before vascular surgery irrespective of their cholesterol levels. (8)

Regimen for management of peri operative blood glucose

It has been shown that peri operative outcome is improved when there is tight control of blood glucose. Most authors now recommend that we should now aim for a blood glucose between 5 and 10mmol/L (90-180mg/dL). (9)

Aside from the type two diabetic undergoing minor surgery, routine management of the diabetic patient should consist of insulin and glucose administration, with the addition of potassium as required.

It has been recommended that the type one diabetic should receive insulin and an infusion of glucose at 5-10g/hr. Insulin can be administered as an infusion or intermittent subcutaneous injection. For the type one diabetic having minor surgery, it is reasonable to administer half their usual morning dose of subcutaneous insulin and an infusion of glucose at 5g/hr. Hourly blood sugar levels are recommended and additional regular insulin given if it is elevated above 11mmol/L. (9)

BSL (mmol/L)	BSL (mg/dL)	Insulin dose
<4.5	<80	Stop insulin infusion (give 10g of glucose)
4.5-10	80-200	1 unit/hr
10-14	200-250	1.5 units/hr
14-17	250-300	2 units/hr
>17	>300	3 units/hr

For the type two diabetic, oral medication is withheld on the day of surgery. The agents with a long half-life such as chlorpropramide should be withheld for 48 hours prior to surgery. Metformin, a biguanide, can cause lactic acidosis, which has a high mortality. Traditionally, it has been recommended that it be ceased for 24 hours pre-operatively, but this has been challenged more recently. If the patient is having minor surgery and there is good pre operative control of blood glucose, it is reasonable to omit the glucose infusion and monitor the blood glucose hourly, administering insulin on an as required basis.

When the type two diabetic is undergoing a major procedure, he or she can be treated with an insulin and dextrose infusion as for a type one diabetic.

The most important part of peri operative glucose management is the regular monitoring of blood glucose concentrations until the patient is tolerating a diet and can have his or her usual medication.

Choice of anaesthetic technique

At present, there is no evidence to suggest that the use of regional anaesthesia with or without general anaesthesia confers any benefit in the diabetic patient in terms of morbidity or mortality. However, there may be some benefits of regional anaesthesia, including the blunting of the stress

response to surgery and earlier return to normal oral intake. A major disadvantage in the diabetic with autonomic neuropathy and the use of neuraxial blockade is profound hypotension, especially in the presence of coronary or cerebrovascular disease. (10)

Conclusion.

Diabetes is increasing in prevalence and we can expect to see more of these patients, particularly the type two diabetic. The anaesthetist is faced with several challenges when looking after these patients, including the increased risk of difficult intubation and aspiration, cardiovascular instability in the patient with autonomic neuropathy, increased cardiovascular complications and the metabolic challenge of ensuring tight blood glucose control. These patients need a thorough preoperative evaluation and may benefit from statin and beta-blocker therapy. Regional anaesthesia may confer some advantages. Perioperative blood glucose control can be achieved using any number of glucose, insulin and potassium regimens. It is now recommended that blood glucose be tightly controlled in the perioperative period to improve outcome.

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ADDENDUM

To convert between mmol/L and mg/dL, 1mmol/L is equal to 18 mg/dL. Divide mg/dL by 18 to get mmol/L and multiply mmol/L by 18 to get mg/dL.

DIABETIC KETOACIDOSIS (DKA).

Principles of treatment

- Resuscitation
- I.V volume replacement
- Insulin
- Prevent hypokalaemia and hyponatraemia.

Clinical assessment

- History and examination
- Check vital signs: HR, BP, JVP, conscious state
- Estimate degree of dehydration
 - 5%: thirsty, dry mucosa
 - 10%: tachycardia, postural hypotension
 - 15% supine hypotension
- Check urea, electrolytes, glucose, ABG every 2 hours until stable
- Check Hct, WCC, LFTs, HbA1C
- Check for primary precipitant: sepsis, AMI, appendicitis, UTI, non compliance etc

Typical early biochemical abnormalities

Hyperglycaemia: 20-40 mmol/L Hyperosmolality: 310-35 mosm

Fluid loss 5-10 litres

Anion gap: > 30

ABGs: pH 6.9-7.15, PCO₂ 8-15mmHg, HCO₃ = 5 mmol/L, lactate = 4-6 mmol/L

Ketoacidosis: acetoacetate = 5 mmol/L, beta hydroxybutyrate = 10-15 mmol/L

Hyperkalaemia = 5-8 mmol/L, total body deficit = 200-700 mmol

Na = 130 mmol/L, Factitious hyponatraemia due to high glucose and lipids,
“corrected” Na = $1/3(\text{glucose}-10) + [\text{Na}^+]$.

Uremia = 25 mmol/L, high creatinine = 0.3-0.5 mmol/L

Elevated free fatty acids = 2-4 mmol/L, hyperuricaemia

Full blood count: high Hct, leukocytoses with left shift.

Treatment

- Large bore IV x2 (central venous catheter useful)
- Give oxygen
- Resuscitate with normal saline or gelofusine
- Calculate
 - Fluid deficit = estimated % dehydration x body weight x 60%
 - Corrected Na⁺ = $1/3(\text{glucose}-10) + [\text{Na}^+]$
 - Corrected K⁺ = $[\text{K}^+] + 5 \times (7.4-\text{pH})$
 - Anion gap = $(\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3)$
- Insulin infusion: infuse at a slow rate, e.g. 0.5-4 units/hour
 - The elderly and children are sensitive to insulin and a rapid fall in glucose and osmolality can result in cerebral oedema
 - Avoid rapid falls in Na⁺, glucose and osmolality, i.e. correct over 48-72 hours.
 - Change to subcutaneous insulin when stable and tolerating oral intake.
- Fluid management
 - One technique is to have two IV lines for fluid replacement. One line is for urine output replacement and one for rehydration.
 - Urine output replacement
 - Use 0.45% saline plus 10mmol KCl/500ml given at the rate of the previous hours urine output less 100 mls until the urine output is less than 100 ml/hr
 - Rehydration
 - Give 50% of estimated deficit in first 8 hours and remaining 50% over 16 hours
 - Options for fluid replacement based on Na and glucose level.

▪ Corrected Na+	▪ <150 mmol/L	▪ >150 mmol/L	▪ >150 mmol/L
▪ Blood Glucose	▪ >20 mmol/L	▪ >20 mmol/L	▪ <20 mmol/L
▪ Replacement fluid	▪ 0.9% saline	▪ 0.45% saline	▪ 4% dextrose 1/5 N/saline

- Use corrected K to estimate severity of K deficit
- Low dose heparin or fully anti-coagulate if elderly or severely dehydrated

HYPEROSMOLAR HYPERGLYCAEMIA.

Hyperosmolar hyperglycaemia occurs primarily in type 2 diabetes and is characterised by marked hyperglycaemia and dehydration (plasma osmolarity over 350 mosm/L) but not ketoacidosis. Disturbances in consciousness vary from drowsy to comatose. It often occurs in elderly patients with previously undiagnosed diabetes and can be precipitated by sepsis. It has a higher mortality than DKA.

Management is similar to DKA but should be administered more slowly with more dilute intravenous fluids (0.45% saline) and lower doses of insulin (0.05 to 0.1 units/kg/hour).

THYROID DISEASE.

The thyroid gland produces thyroid hormone and calcitonin and its main function is to regulate metabolism with a small contribution to calcium haemostasis. The thyroid hormones bind to specific receptors in the nuclei of target tissue cells and are involved in metabolism (and therefore oxygen consumption), thermogenesis, growth and myelination in childhood. (1)

Triiodothyronine (T3) and thyroxine (T4) are produced from iodide and thyroglobulin in the thyroid gland. T3 is approximately 4 times more potent than T4 but its half-life is shorter. There is some peripheral conversion of T4 to T3 in the tissues. (TSH) Thyroid stimulating hormone from the anterior pituitary is released in response to falling levels of the thyroid hormones. TSH acts on the thyroid to stimulate production and release of T3 and T4. TSH production is also stimulated by thyrotropin releasing hormone (TRH), which is produced by the hypothalamus. T3 and T4 act to inhibit release of TSH and TRH to provide a negative feedback mechanism. Autoregulation of the thyroid is another factor that controls the secretion of thyroid hormones. It adjusts for the range of iodide in the diet. Large doses of iodine will inhibit the release of thyroglobulin bound hormones and reduce the vascularity of the thyroid and can be used in the management of hyperthyroidism. This is the Wolff-Chaikoff effect. (1) (2)

Hyper and hypothyroidism have many clinical manifestations and will have implications for anaesthesia. Goitre may be present in the presence of either hyper or hypothyroidism or without any overt symptoms of glandular dysfunction. The thyroid is normally situated in the anterior neck with its isthmus across the second and third tracheal rings. This has implications for airway management, particularly when there is gross enlargement of the gland, which can cause compressive symptoms and distortion of the airway, as well as obstruction to venous return from the head and neck. Our main concerns as anaesthetists will be to ensure the patient is euthyroid and that we can deal with the establishment and maintenance of a secure airway during and after surgery. One should also bear in mind that there could be other co-existing endocrinopathy present.

Hyperthyroidism.

Hyperthyroidism occurs due to the increased concentrations of T3, T4 or both in the circulation. It manifests as anxiety, weight loss in spite of adequate calorific intake, fatigue, muscle weakness, tremor and heat intolerance. Goitre is usually present. Tachycardia can give rise to palpitations and atrial fibrillation, angina or congestive cardiac failure may become apparent. The circulation becomes hyperdynamic due to increased sympathetic nervous system activity and vasodilatation from the body's attempt to eliminate excess heat. There is an increased sensitivity of beta-receptors and the adrenal cortex produces and uses more cortisol. The presence of eye signs such as exophthalmos may reflect the cause (Grave's disease).

The causes of hyperthyroidism are classically, Graves's disease, toxic multinodular goitre or a toxic thyroid adenoma. It may occur in pregnancy (0.2%) and is most commonly due to diffuse toxic goitre. (3) There may be a brief period of hyperthyroidism in the patient with thyroiditis. Grave's disease is caused by a thyroid-stimulating immunoglobulin, which binds to the TSH receptor. It may be associated with diffuse goitre, pretibial myxoedema and exophthalmos. (4)

The diagnosis is made based on high levels of T3 and T4 with a reduced TSH level. In secondary hyperthyroidism, the TSH level will also be raised.

The treatment of hyperthyroidism is geared towards a return to the euthyroid state. This may not be possible without surgery, so the anaesthetist should expect to deal with some patients whose thyroid disease is not well controlled. The treatment options involve antithyroid drugs, radioactive iodine and thyroid surgery. The patient with thyroid disease needs to be followed up indefinitely, because there is the chance that hypothyroidism may develop, or a recurrence of hyperthyroidism may occur.

Antithyroid drugs include propylthiouracil (PTU) and methimazole (or carbimazole, which is metabolised to methimazole). These drugs inhibit oxidation of inorganic iodine and its incorporation into tyrosine, that is, they inhibit synthesis of new hormone but have no effect on the glandular release of preformed hormone. (7) PTU also decreases the conversion of T4 into T3 in the periphery. Patients become euthyroid over several months, but the effects of these drugs are seen after 3-4 weeks. One of the more serious side effects is agranulocytosis, which can cause infective and bleeding problems. (3)

Beta antagonists can be used to control the symptoms of hyperthyroidism. They are effective within 12-24 hours of commencement of therapy. Their main effect is produced due to beta-blockade but propranolol is also able to inhibit the conversion of T4 into T3 in the tissues. (4)

Ablative therapy is achieved with radioactive iodine (I131), which concentrates in the thyroid and destroys functioning cells. It takes 6-10 weeks to produce a clinical effect and repeat doses may be required. There are few side effects apart from hypothyroidism. (4)

Subtotal thyroidectomy can induce disease remission in most patients with Grave's disease. (3) Ideally, any patient with hyperthyroidism should be rendered euthyroid before surgery with medication. This may not be achievable in all patients, and an attempt to control the cardiovascular symptoms with beta-blockade is usually made.

The complications of thyroid surgery include incomplete control of the hyperthyroidism, hypothyroidism, recurrent laryngeal nerve damage and tracheal compression. Airway obstruction can occur after the resection of a large goitre due to tracheomalacia or postoperative bleeding into the neck. Hypoparathyroidism due to accidental removal of the parathyroid glands and hypocalcaemia usually manifests 24-72 hours later, but may present as laryngospasm in 1-3 hours postoperatively.

Thyroid storm (thyrotoxicosis) is a life-threatening exacerbation of hyperthyroidism with an abrupt onset. It is usually precipitated by stress such as surgery or infection. It constitutes a medical emergency and treatment should be commenced before laboratory confirmation. Its

features are fever, increased cellular metabolism with resultant increased carbon dioxide production and acidosis, tachycardia arrhythmias, congestive cardiac failure and shock, agitation, delirium and coma, diarrhoea, vomiting and abdominal pain. (4) The mortality rate is 10-20%. (5)

It is diagnosed on clinical presentation and is confirmed by increased levels of T3 and T4 with very low or undetectable levels of TSH. The levels of T3 and T4 do not correlate well with the severity of the condition. (5)

The fever may be extreme (>41 degrees Celsius) and the skin is usually moist and warm. Thyrotoxicosis has been confused with malignant hyperthermia and the symptoms have been successfully managed with dantrolene. (5)

Cardiovascular features of thyrotoxicosis are very common. Sinus tachycardia with a rate over 160 beats per minute, heart failure, atrial fibrillation and ventricular arrhythmias occur. There may be cardiomegaly and ECG changes of left ventricular hypertrophy. (5)

Neuromuscular disturbances are also frequently seen. Tremor with increasing restlessness progresses to delirium, coma and death if left untreated. Hypercalcaemia occurs in 15% but is rarely a separate emergency. Other electrolyte disturbances include hypokalaemia and hypomagnesaemia. (5)

The management of thyrotoxicosis includes supportive measures such as oxygen therapy, fluid, electrolyte and glucose administration, cardiovascular monitoring and treatment and cooling of the patient. The synthesis, release and peripheral conversion and peripheral effects of thyroid hormones are blocked with medication. Beta-blockers are used to treat the tachycardia, fever, and tremor and to reduce the peripheral conversion of T4 to T3 (propranolol). Large doses may be required, due to altered pharmacokinetics, in particular, increased clearance of the drugs. Beta-blockers are combined with other therapy, since the basic metabolic abnormality is not inhibited. Corticosteroids are administered due to a relative deficiency and glucocorticoids may inhibit peripheral conversion of T4 to T3. (5)

Antithyroid medications are not available as parenteral preparations and are administered orally or via a nasogastric tube. Absorption may be unreliable in the presence of gastrointestinal symptoms. Propylthiouracil has a more rapid onset of action than methimazole or carbimazole (within one hour). (7)

Inorganic iodine is only administered after the administration of the antithyroid medications in order to prevent a rise in thyroid hormone levels. High concentrations of inorganic iodine directly inhibit release of T3 and T4 from the gland and transiently inhibit new hormone synthesis. (7) It can be given orally as Lugol's iodine, potassium iodide or sodium iodide. Intravenous contrast can be given and they act to lessen the cardiac effects of thyroxine as well as to block conversion of T4 to T3. (5) If the patient is allergic to iodine, lithium can be used. (4) The effects of iodine occur immediately, but last for only several weeks. It is useful in the preparation of the patient for thyroid surgery. (7)

Digoxin and amiodarone may be required to treat the atrial fibrillation and vasopressor therapy may be required for the patient who has developed circulatory shock.

Anaesthetic implications of hyperthyroidism.

Except in an absolute emergency, patients with hyperthyroidism should be rendered euthyroid prior to surgery. This may take more than 6 weeks. Beta-blockade combined with iodide or lithium can achieve the euthyroid state in 1-2 weeks, but the cardiac effects of hyperthyroidism may take longer to resolve. (4) Iodide should be combined with antithyroid medication to avoid exacerbation of the hyperthyroid state. There is an increased risk of cardiac failure, arrhythmias and thyroid storm in these patients.

If emergency surgery is required, commence an antithyroid medication and provide preoperative sedation. Intraoperative management includes monitoring of temperature, heart rate, blood pressure (intra arterial if possible), end tidal carbon dioxide and oxygen saturations. It would be desirable to measure arterial blood gases if this is available. Sympathetic stimulation should be avoided. Some medications to avoid include, ketamine, pancuronium, and adrenaline-containing local anaesthetic agents. Anticholinergics are avoided because they may precipitate tachycardia and alter heat regulation to worsen hyperthermia. (7) Beta-blockers should be continued to control the heart rate. There may appear to be an increased volatile anaesthetic requirement. This is due to an increased cardiac output and increased temperature. An adequate depth of anaesthesia is required to reduce the stress response. The eyes should be protected. Reversal of neuromuscular paralysis should include glycopyrrolate rather than atropine. A regional technique can be considered to decrease sympathetic stimulation. Treatment of hypotension will require a direct acting vasoconstrictor such as phenylephrine or metaraminol. If ephedrine, adrenaline or noradrenaline need to be used, they are given in very small doses. Postoperatively, intensive monitoring is required to detect and treat thyroid storm. (4)

Hypothyroidism.

Primary hypothyroidism causes a decreased production of thyroid hormones in the presence of adequate or increased levels of TSH and accounts for 95% of all cases of hypothyroidism. (7) The most common causes in the developed world are ablation of the gland by radioactive iodine, surgery or thyroiditis but reduced levels of iodine in the diet cause hypothyroidism in the developing world. Hypothyroidism may occur secondary to pituitary insufficiency, which results in an inappropriately low TSH. (4)

The incidence of hypothyroidism depends on the level of iodide in the diet, with a higher incidence in areas with endemic low levels of iodide. In these populations, there is an increased risk of goitre, sub fertility and neonatal hypothyroidism, which can lead to mental retardation.

Hypothyroidism results in depression of cardiac function, decreased spontaneous ventilation, abnormal baroreceptor function, reduced plasma volume, anaemia, hypoglycaemia, hyponatraemia and impaired hepatic drug metabolism. (8)

Common clinical manifestations of hypothyroidism include sensitivity to cold, weight gain, amenorrhoea, dry skin, alopecia, pallor, puffy eyelids, large tongue, and husky voice (due to the accumulation of mucopolysaccharides in the skin). (4) There is bradycardia, decreased stroke

volume, cardiac enlargement (with or without a pericardial effusion), and heart failure. Coronary artery disease is often present. (4) There is a decreased cardiac output with an increase in systemic vascular resistance and decreased blood volume, which results in a narrow pulse pressure and prolonged circulation time. (3)

End organ responses to catecholamines are altered and there is a reduction in beta-receptor activity as well as number. (7) Maximum breathing capacity and diffusion capacity are decreased and there is a decreased ventilatory response to hypoxia and hypercarbia. (7) There is a slowing in mental function and frank psychosis can be present. In the gastrointestinal system, constipation and delayed gastric emptying occur. (4)

Myxoedema coma occurs rarely. It is severe hypothyroidism characterized by coma, hypoventilation, hypothermia, bradycardia, hypotension and dilutional hyponatraemia. It is a medical emergency with a mortality rate of 15-20%. Triggers include, infection, exposure to cold, trauma and central nervous depressants. It occurs more commonly in the elderly. (7) Treatment includes the intravenous administration of thyroid hormones, passive warming and supportive measures. Intubation and ventilation may be required if there is severe respiratory depression or the patient cannot maintain his or her airway. Intravenous fluids are given and electrolyte imbalances are corrected. As the patient warms, vasodilatation may cause a fall in venous return and a drop in blood pressure. Intravenous hydrocortisone is given to treat possible adrenal insufficiency. (7)

Anaesthetic implications of hypothyroidism.

Ideally, hypothyroid patients will be rendered euthyroid with thyroxine before surgery. However, it is only the patients with moderate to severe disease that exhibit major problems, and it is likely that many patients have subclinical hypothyroidism so that we are unwittingly anaesthetising such patients regularly. In the patients with severe hypothyroidism who need to undergo emergency surgery, the potential for severe cardiovascular instability and myxoedema coma is high. (7)

The half-life of thyroxine is seven days, and it may not have an effect for some time after administration. The half-life of T3 is only 1.5 days, so a combination of T4 and T3 are given in the management of myxoedematous coma. (8) The administration of thyroxine needs to be very careful, as it may precipitate ischaemia in the patient at risk of ischaemic heart disease. (8) In patients with severe hypothyroidism but not coma, the emphasis is on low doses of thyroxine with a gradual escalation in the dose over several weeks to eventually reach a euthyroid state. The patient with coronary artery disease may not tolerate this and may need their coronary artery disease treated before they are euthyroid.

In the patient that is clinically hypothyroid, it would be sensible to avoid premedication and to limit the use of respiratory depressant medications. Regional anaesthesia is preferable. The doses of medications used for anaesthesia should be lowered and titrated to effect, as there is a reduction in clearance of medication as well as sensitivity to sedative agents. There appears to be an increased sensitivity to inhalation agents, but this is likely to be related to a reduced cardiac

output, reduced blood volume, abnormal baroreceptor function, decreased hepatic metabolism and renal excretion rather than a reduction in MAC (minimum alveolar concentration). (7)

Airway compromise can occur due to myxoedematous swelling of the vocal cords and upper airway, macroglossia or the presence of goitre. Gastric emptying is delayed, which increases the risk for aspiration.

Hypothermia is a common problem in the hypothyroid patient undergoing anaesthesia and attempts to maintain heat or warm the patient need to be made.

Neuromuscular dysfunction with weakened respiratory muscles occurs in hypothyroidism. Anaesthetic agents can make this worse. (7)

Ketamine is the preferred induction agent, as it will support the blood pressure and heart rate. For maintenance, nitrous oxide in oxygen (70:30), with small doses of short-acting opioid (eg fentanyl) or benzodiazepine or ketamine can be used. Intermediate or short-acting neuromuscular blockers are preferable and controlled ventilation is recommended to minimize carbon dioxide retention from hypoventilation.

Hypotension is best treated with ephedrine and not a pure alpha-agonist because an increase in systemic vascular resistance is not desirable in a heart with reduced contractility. (3) (7) The increased incidence of adrenocortical insufficiency makes it necessary to administer hydrocortisone to cover periods of surgical stress. (8)

Careful positioning of the patients undergoing anaesthesia is important, as these patients may have a pre-existing neuropathy secondary to oedematous tissues.

Recovery from anaesthesia may be delayed due to the increased sensitivity to sedative agents. Pain relief is best provided with regional techniques and non-opioid analgesics.

Thyroid surgery.

The indications for thyroidectomy include malignancy, goitre with obstructive symptoms, retrosternal goitre, hyperthyroidism that is not responsive to medical treatment, recurrent hyperthyroidism, and Hashimoto's disease if there is a superimposed lymphoma. (8)

Preoperative assessment will focus on the identification of thyroid dysfunction (either hyper or hypothyroidism), associated medical conditions (such as phaeochromocytoma in the presence of medullary cancer), assessment of the airway and presence of tracheal or venous obstruction.

Investigations may include thyroid function testing, haemoglobin, white cell and platelet counts, urea and electrolytes, calcium, chest x-ray (looking for tracheal deviation and compression) or computerized tomography (CT) (to assess retrosternal extension) and indirect laryngoscopy (to check for vocal cord dysfunction).

Thyroidectomy can be performed under a regional technique, but this can be complicated by bilateral phrenic nerve block if bilateral deep cervical plexus block is used. More commonly, general anaesthesia is performed.

A relaxant general anaesthetic with endotracheal extubation is commonly performed. The endotracheal tube should not kink as it reaches body temperature, needs to be out of the surgical field and may need to be a size smaller than usual due to tracheal narrowing. A small, reinforced tube is commonly chosen. Laryngeal mask anaesthesia can be employed but is relatively contraindicated if there is tracheal compression or deviation. There is also the risk that the surgeon may displace it during the operation.

Difficult intubation is more likely if there is a large goitre present. Indeed, 6% of tracheal intubations for thyroid surgery are difficult. (8) An inhalation induction may be used or awake fibreoptic intubation is preferred when it is available. The endotracheal tube should be positioned so that the cuff is beyond the point of extrinsic compression when it is present. (4)

The patient is usually positioned with towels or padding between the shoulders and the head rests on a head ring with the neck extended for easy surgical access. The arms are positioned by the patient's sides to allow the surgeon and assistant to stand beside the patient. The head of the table is tilted to assist venous drainage. This position makes it difficult for the anaesthetist to gain access to the airway and arms.

The surgeon may infiltrate the skin with adrenaline-containing local anaesthetic to provide a 'bloodless' field. Care must be taken if halothane is being used, as large doses of adrenaline will cause arrhythmias.

At the end of the operation, the patient is extubated when the airway reflexes return and coughing should be prevented when possible. Nursing the patient with the head of the bed elevated when he is awake allows for better venous drainage. The patient should be carefully observed for the development of a neck haematoma, as this will cause compression of the airway and will necessitate a return to the operating room. For the patient who has had a large goitre removed, one should be vigilant for the development of obstruction due to tracheomalacia. The patients with thyroid cancer have a greater risk of developing recurrent laryngeal nerve damage during surgery. Bilateral vocal cord paralysis will lead to stridor at extubation and reintubation will be required.

Hypocalcaemia is most likely to occur 36 hours after the operation, and only 3.1% of patients will remain permanently hypocalcaemic. Postoperative pain is not generally a major problem and many patients will require minimal analgesia. Thyroid storm classically occurs 6-18 hours postoperatively, but may present intraoperatively. (6)

In summary, it is likely that the anaesthetist will be faced with patients presenting for surgery in the presence of thyroid disease. Most commonly it will be in the context of thyroidectomy, but it may be for unrelated surgery. Ideally, the patient will be euthyroid at the time of surgery. Airway management may present a significant challenge. Postoperative complications can include endocrine complications as well as airway obstruction. Adequate postoperative monitoring is essential in order to allow for early detection of these complications.

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PHAEOCHROMOCYTOMA.

Background.

Phaeochromocytomas are rare, functionally active, catecholamine secreting neuroendocrine tumours.(1) They are of particular clinical interest due to the marked physiological changes they produce, due to the release of large quantities of catecholamines.(1)

They can arise from chromaffin cells of the:

- Adrenal medulla.
- Extra-adrenal paraganglia.
- Chromaffin cells originate from the embryonic neural crest tissue (and can be found anywhere between the skull to the anus).(1) (2)

Chromaffin tissue can also occur in the coeliac, mesenteric, renal, adrenal, hypogastric, testicular and paravertebral sympathetic nervous plexuses (2)

Tumours arising in the adrenal medulla produce and secrete adrenaline and noradrenaline, however, noradrenaline is usually the predominant catecholamine released (2) Extra-adrenal tumours only liberate noradrenaline (they lack the enzyme required to convert noradrenaline to adrenaline).

Phaeochromocytomas have a highly variable clinical presentation and have been referred to as the 'great mimickers' in clinical medicine.**Error! Bookmark not defined.Error! Bookmark not defined.** The most common clinical manifestations include episodic headache, sweating, palpitations and excessive or severe hypertension. (1)

The potent systemic effects of the secreted catecholamines from these tumours are responsible for the serious and potentially lethal cardiovascular manifestations seen in this condition. (1)

Prognosis is excellent following prompt diagnosis, pre-operative pharmacological management and tumour removal however, the prognosis is somewhat poorer if the patient has metastatic disease, which can occur with larger tumours or extra-adrenal tumours (1)

The majority of phaeochromocytomas are isolated tumours (90% of cases), but they can be associated with or part of an autosomal-dominant (familial) multiglandular neoplastic syndrome series: medullary thyroid carcinoma, Von Recklinghausen disease and Von Hippel-Lindau syndrome (1) (2).

Incidence.

Approximately 80-85% of phaeochromocytomas originate in the adrenal medullae. Some 15-20% arise from the extra-adrenal chromaffin tissue. (1). Other sources suggests that only 6% of tumours are extra-adrenal (4) (5)

Phaeochromocytomas can arise anywhere in the body where paraganglion cells of the sympathetic nervous system are located. The tumour is benign and unilateral (localized in a single adrenal gland) in up to 90% of cases, however: 10-15% are bilateral (or extra-adrenal). **Error! Bookmark not defined.** Bilateral tumours also tend to be familial. 10-30% are malignant. Approximately 90% of phaeochromocytomas are benign and amenable to surgical removal. (2) (3) (4) However some tumours are unresectable.

They can occur in any age group, but a higher incidence is found during the 4th and 5th decade of life. 10% of all diagnoses are made in children with a higher male predominance, They are often extra-adrenal, multifocal and associated with one of the hereditary/inherited syndromes. (1) 35-70% of phaeochromocytomas in children are multiple and extra-adrenal (compared with 8 - 15% in adults). The prevalence of malignancy is lower in children. 70%. Adults show a female predominance, 55-60%. (2) (4)

Hypertension is a common finding in general practice and hospital patient populations however, the prevalence of phaeochromocytomas in patients with hypertension is very low at 0.1-0.6%. (1) (2) (3) (4)

Catecholamine Physiology.

Phaeochromocytomas can secrete either or all the catecholamines: adrenaline, noradrenaline and dopamine. With adrenaline secreting tumours, 15% only secrete the catecholamine paroxysmally, producing episodic symptoms. (1)

Catecholamines are a group of substances containing catechol (benzene ring with OH (hydroxyl) groups at positions 3 and 4) and amine portions (see figure 1). They act at adrenergic receptors in the central nervous system and sympathetic nervous system (See Table 1). (6)

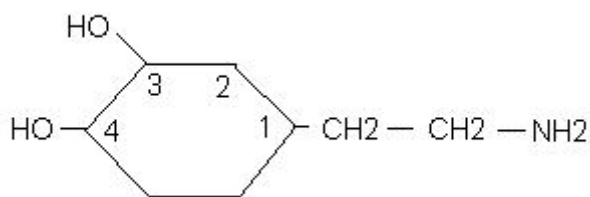


Figure 1: Catecholamine structure (dopamine in this example).

Only noradrenaline is released from post-ganglionic sympathetic neurons as a neurotransmitter.

Both adrenaline and noradrenaline are synthesized in the adrenal medulla. Adrenaline is not produced in sympathetic adrenergic nerve terminals, only dopamine and noradrenaline are produced here.

Table 1. Classification and action of adrenergic receptors (abbreviated). (6)

<u>Receptor subclass</u>	<u>Site</u>	<u>Effect of stimulation</u>
Alpha 1	Vasc. Smooth muscle Liver	Contraction Glycogenolysis
Alpha 2	Presynaptic adrenergic synapses Pancreatic islet cells	Reduced noradrenaline release Inhibits insulin secretion
Beta 1	Heart	Increased rate/force contract.
Beta 2	Vasc. Smooth muscle Bronchial smooth musc.	Relaxation (muscle beds) Relaxation

Taken from: Yentis SM, Hirsch NP, Smith GB. Anaesthesia and Intensive Care. 3rd Ed. Butterworth Heinemann, 2004.

Synthesis of naturally occurring catecholamines proceeds in many steps commencing with either phenylalanine or tyrosine. The formation of dopamine occurs in the cytoplasm of the cell from tyrosine via dihydroxyphenylalanine. Dopamine is taken up into vesicles and converted into noradrenaline. The noradrenaline is stored in distinct secretory granules

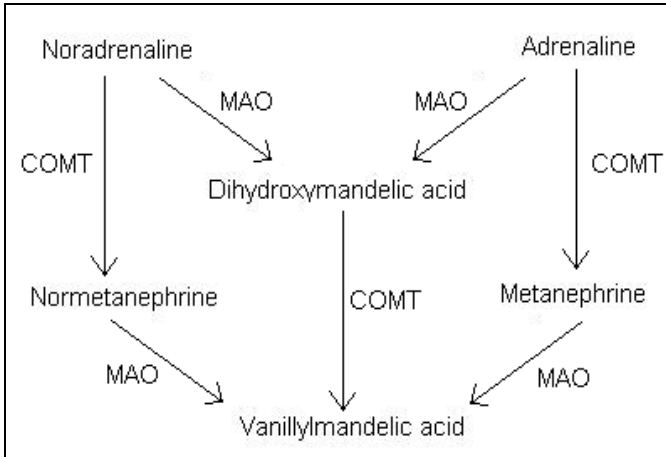
Adrenaline is only produced in specialized cells (the phaeochromocytes) of the adrenal medulla where noradrenaline is converted by phenylethanolamine N-methyltransferase to Adrenaline.

The termination of the effect of catecholamines released at adrenergic nerve terminals is achieved predominately by an active reuptake mechanism, whereby the neurotransmitter is recycled back into the nerve terminal.

Additionally, two enzyme systems exist that metabolise any catecholamine that is not recycled by reuptake into inactive metabolites (see figure 2). Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). The inactive metabolites are then excreted in the urine.

Dopamine is metabolized to homovanillic acid (HVA).

Figure 2. Metabolism pathway for catecholamines. (2)



Adapted from: Pullerits J, Ein S, Balfe JW. Anaesthesia for pheochromocytoma. Canadian Journal of Anaesthesia 1988; 35:5 pp526-534.

Clinical Presentation/Manifestations.

Pheochromocytomas can produce wide and variable clinical manifestations and has been referred to as the “great mimicker” in clinical medicine. (2) (4) (5). The differential diagnosis therefore, has to be carefully considered. Signs and symptoms seen with pheochromocytomas reflect an excess of circulating concentrations of noradrenaline, adrenaline and dopamine concentration. (5) The clinical manifestations can depend upon the predominant catecholamine secreted by the tumour e.g. adrenaline, noradrenaline or dopamine. Noradrenaline secreting tumours typically present with hypertension. Adrenaline and dopamine secreting tumours present with a wider variety of symptoms (such as palpitations, tachycardia, anxiety and nervousness). (5)

The size of the tumour also plays a role. Small tumours tend to produce episodic hypertension with periods of normal blood pressure in between. Larger tumours tend to produce chronic or sustained hypertension.

Due to episodic release of catecholamines from pheochromocytomas, paroxysmal signs and symptoms are frequently seen and provide a useful clue as to the diagnosis. Most commonly, patients are found to be severely hypertensive and describe headaches (secondary to hypertension), palpitations, tachycardia, anxiety and excessive sweating (see table 2).

Hypertension can have a varied presentation. Some patients have episodic hypertension on a background of chronically sustained high blood pressure Some patients have episodically elevated blood pressure but with normal pressure between episodes. (1)

Table 2. Frequency of signs and symptoms of phaeochromocytomas. (1)

Sign(s)/Symptom(s)	Frequency seen (% patients)
Headache	60-90
Palpitations	50-70
Sweating	55-75
Pallor	40-45
Nausea	20-40
Flushing	10-20
Weight Loss	20-40
Tiredness	25-40
Anxiety/Panic disorder	20-40
Hypertension – sustained	50-60
Hypertension – episodic/paroxysmal	30
Hypertension – orthostatic/postural	10-50
Hyperglycaemia	40

Taken and adapted from: Lenders JMW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005; 665-675.

In as many as up to 60% of patients with phaeochromocytoma, significant (toxic) cardiomyopathy is found and this can result in a high mortality rate. This can produce cardiac dysrhythmias, congestive cardiac failure, or acute pulmonary oedema. (2)

Chronic or prolonged exposure to increased circulating levels of catecholamines, in particular noradrenaline, results in significant arteriolar and venous constriction which results in a marked decrease in the circulating blood volume. (5)

Diagnosis and Investigations.

Consider the diagnosis of phaeochromocytoma in any patient with hypertension developing at an early age, hypertension resistant to conventional pharmacological therapy or episodic headaches, sweating, palpitations or pallor. Due to episodic release of catecholamines from phaeochromocytomas, paroxysmal signs and symptoms are frequently seen and provide a useful clue as to the diagnosis (especially with adrenaline only secreting tumours). (1)

All patients with a suspected phaeochromocytoma should undergo formal biochemical testing to confirm the diagnosis. Once the combination of signs and symptoms has alerted to a diagnosis of phaeochromocytoma the best confirmatory biochemical test is to measure the free catecholamine levels in the urine over a 24-hour period. (5)

Other sources state that plasma catecholamine concentrations are the best indicator (4) or that measurements of plasma free-metanephrines or urinary fractionated-metanephrines are the most sensitive tests for diagnosis. (1)

Imaging techniques are next employed to localize the tumour once a biochemical diagnosis is confirmed. CT and MRI are frequently used and very sensitive detecting tumours as small as 1cm in diameter. Meta-iodobenzyl guanidine (MIBG) is a radiopharmaceutical agent that can be used to localize recurrent tumours, metastases and tumours in unusual sites (such as the bladder or pericardium). (5) It is actively taken up into chromaffin storage granules. It can be then detected using a gamma imaging camera. (4)

As soon as a diagnosis is made, pharmacological therapy should be introduced to protect the patient from the dangers of elevated catecholamine levels. (4)

Routine ECG should be undertaken, and can show

- Dysrhythmias.
- Myocardial ischaemia/infarction.
- Signs of ventricular hypertrophy. (2)

Blood glucose should also be requested, as up to 60% of patients will have hyperglycaemia, but often do not require insulin. (2) High catecholamines result in glycogenolysis, inhibition of insulin secretion from pancreatic beta islet cells (beta stimulation actually promotes insulin release but the alpha effect predominates) and lipolysis. (4)

Chest X-ray may show signs of congestive cardiac failure.

Due to elevated circulating catecholamines and the vasoconstriction they induce, the circulating blood volume is often contracted and diminished. This can be seen by measuring the patient's haematocrit. If the haematocrit is > 0.45 , it gives a good indication that the blood volume is significantly contracted. (2)

Pre-Anaesthetic and Pre-Surgical Pharmacological Management.

Surgery is the only curative measure with pheochromocytoma, however pharmacological management of the high circulating levels of catecholamines and their subsequent end organ effects are very important, prior to surgery. (5)

Due to the rarity of cases of pheochromocytoma, there are no randomized prospective control trials of sufficient size that have established the most effective drug or drug regime pre-operatively. (1) Current regimes are based on tradition and clinician experience.

The main goal of pre-operative pharmacological treatment is to prevent catecholamine induced swings in blood pressure, arrhythmias and pulmonary oedema that can occur during surgery with manipulation of the tumour. (1) Pre-operative pharmacological treatment is typically instigated on an outpatient basis.

The ideal pre-operative treatment duration has not been determined in any randomized controlled trials, but most patients receive 10-14 days of treatment and treatment is recommended to continue up until the night before surgery. (1)

The other main goals of pre-operative therapy are

- To control systolic (and diastolic) blood pressure, via adequate alpha blockade.
- To control the heart rate (tachycardia).
- To treat any coexistent dysrhythmias.
- To re-expand and restore, or allow the contracted blood volume to be restored to normal, by the body.

Pharmacological therapy should be continued up until 2200 hours the night before surgery, if the surgical start time is 0830 hours the following day.

Alpha-adrenoreceptor antagonists

Many review papers agree that patients with pheochromocytomas benefit from alpha blocking agents pre-operatively however, evidence from randomized control trials is lacking due to the rarity of the condition.

Phenoxybenzamine.

Is a non-competitive, non-selective alpha adreno-receptor antagonist, that forms an irreversible covalent bond with the alpha-receptor on vascular smooth muscle producing vasodilatation. It has been the mainstay of therapy (used since 1950's) and may take 24-36 hours to produce an effect. The long half-life of 24 hours, allows twice daily administration.

Initial dose recommended is 10mg twice daily. The dose can be increased every 2-3 days by up to 10-20mg to a total daily dose 1mg/kg. It is recommended that phenoxybenzamine be continued up until the day of surgery.

Other regimes suggest 10mg oral twice daily, increased to 10mg three times daily on day 2. The dose is then adjusted on an individual basis. In this retrospective study, the highest dose was 20mg three times daily. (9)

Side effects include orthostatic hypotension, reflex tachycardia, pupillary constriction, nausea, sedation (alpha2 effect), weakness and nasal stuffiness. Disadvantages include alpha2 blockade (non-selective alpha blocker) at presynaptic terminals that can increase noradrenaline release and increase the heart rate and force of contraction. (5) These symptoms are commonly treated with beta-blocking agents.

Doxazosin.

Prys-Roberts advocates the use of Doxazosin over Phenoxybenzamine. (5) In 20 patients in this series, blood pressure control was at least as good as that achieved with phenoxybenzamine. Only 9 patients of the 20 required adjunctive beta-blockade.

This drug is a competitive alpha adrenoreceptor blocker and selective for alpha1 adrenoreceptors. As it is a competitive blocker it can therefore be displaced from receptors by high levels of circulating catecholamines.

Doxazosin is non-lipophilic and therefore does not readily cross the blood brain barrier. It has high bioavailability and a long duration of action allowing once daily administration. The introductory dose is 1mg daily and can be increased to up to 16mg daily. (5)

Some studies have shown that this drug is associated with less hypotension post-operatively. Due to the lack of alpha2 blockade mediated reflex tachycardia, beta blockers are often not required in patients treated with Doxazosin. (5)

Prazosin.

Prazosin is a competitive Alpha1-selective blocking agent with a short half-life and high first pass metabolism. It does not adequately prevent perioperative hypertensive crises. (2) (5) (9) Initial starting with a dose of 1mg 8 hourly and gradually increase to 12mg daily. (5)

Beta-blocking agents.

These agents are useful for treating patients with tachyarrhythmias and one group believe that they need not be used routinely and are only indicated if the patients have significant dysrhythmias or tachycardia. (2)

The 2 reasons to use beta-blockers are:

- To reduce the symptoms of increased plasma catecholamines (e.g. tachycardia or arrhythmia). (5)
- To block any alpha2 induced cardiac sympathetic drive due to phenoxybenzamine administration.
-

If considering the use of beta blocking drugs, they should be introduced only after several days treatment with an alpha blocking drug. It is very important not to introduce beta-blockade before alpha-blockade. The loss of beta 2 mediated vasodilatation of vessels, especially in muscle beds, leaves stimulation of alpha receptors by catecholamines unopposed and potentially leads to hypertensive crises. Beta blockers should also be cautiously used if the patient has known cardiomyopathy as use may precipitate congestive cardiac failure.

Regimes described include:

- Propranolol 120 – 160mg bd.
- Atenolol 25 - 100mg daily.
- Metoprolol 50 - 150mg tds (1)

Labetolol.

Labetolol is a combined beta and alpha blocking agent (2:1 to 5:1 ratio of alpha to beta). (7) It is alpha 1 selective, but a non-selective beta receptors. Labetolol can be used in combination with pure alpha blocker however it does not adequately prevent hypertension with large releases of catecholamines when used alone. (2) (9)

The half-life is 4 hours with extensive first pass metabolism when administered orally.

Adequacy of pre-operative pharmacological treatment is indicated by the following:

- Decrease in blood pressure to below 160/90 mmHg is recommended for at least 24 hours pre-operatively. (1)
- Presence of orthostatic hypotension. (A small retrospective study has shown however, that a postural drop in blood pressure does not correlate with perioperative stability. (9))
- Nasal stuffiness
- ECG: No greater than one ventricular premature beat (extrasystole) and ST changes for 5-7 days. (8)

As the vascular system reexpands with the introduction of alpha blockade, an extracellular compartment (vascular) fluid deficit often develops. This can be treated by increasing the patient's oral fluid and salt intake. (1)

Intraoperative Pharmacological Management.

Drugs that induce the release of histamine have been discussed in many articles, since histamine can induce the release of catecholamines from chromaffin granules. (5) However both morphine and atracurium (both known to release histamine) have been used safely during anaesthesia for phaeochromocytomas.

Despite adequate and appropriate pre-operative pharmacological management of patients with phaeochromocytomas, large swings in blood pressure can still occur during surgery, especially at anaesthetic induction, manipulation of the tumour and following ligation of the venous drainage of the tumour.

Drugs that have been used include:

Phentolamine a non-selective alpha antagonist, with additional direct relaxant effects on vascular smooth muscle has little place in pre-operative pharmacological therapy, but useful in the treatment of intra-operative hypertension. The dose is 1-2mg IV to treat hypertension associated with tumour manipulation and acts within 2-5 minutes and duration of action is 10-15 minutes. (7)

Magnesium sulphate is a potent vasodilator (relaxes vascular smooth muscle). Although an essential cofactor for the inotropic effect of catecholamines, magnesium attenuates the vasoconstrictor and pro-arrhythmogenic effects of catecholamines and also inhibits catecholamine release from the adrenal medulla. It has been used in the intra-operative management of phaeochromocytoma to attenuate increases in blood pressure. (5)

Suggested doses are:

- Loading with 40-60mg/kg followed by an infusion of 1-2g/hour. (5)

As yet, no randomized control trials have been conducted.

Other drugs:

Beta-blockers: Labetolol has been used intra-operatively. Esmolol is also used, favoured for its brevity of action.

Calcium channel blockers: When used alone do not fully prevent haemodynamic instability but can be used in combination with alpha-blockers.

Sodium nitroprusside: Has been used by many anaesthetists due to its rapid onset of action and short duration of action but it also has significant metabolic consequences and toxicity (cyanide and thiocyanate).

Post-operative Problems.

There are 3 important post-operative problems that occur commonly after resection of a pheochromocytoma: Hypertension (exacerbated by pain, hypoxia, hypercarbia, urinary retention), hypotension (infrequent if the patient is appropriately alpha-blocked pre-operatively and intravascular volume has been adequately replaced. This is due to the continued pharmacological blockade and sudden reduction of circulating plasma catecholamines) and hypoglycaemia. Catecholamines inhibit insulin release from beta cells in the pancreas via alpha-receptor activation causing pre- and intra-operative hyperglycaemia. After tumour resection, beta-cell function recovers and insulin is secreted producing hypoglycaemia. (2)

Anaesthetic Implications.

Pheochromocytoma is one of the great challenges to anaesthetists both pre- and post-operatively. It is of vital importance to diagnose a pheochromocytoma before any anaesthesia or surgery. Emergency surgery to remove a pheochromocytoma should never be attempted in a patient that has not been adequately prepared pre-operatively. (4) Mortality for emergency presentation is approximately 50%, whereas mortality for elective surgery is less than 2%. (8)

In an undiagnosed pheochromocytoma unexpected and marked intra-operative hypertension and tachycardia are typically the first indications of the condition. (3) Importantly, when an unanticipated pheochromocytoma manifests intra-operatively, even if it is a seemingly short or simple procedure, the mortality rate is approximately 50%. This contrasts with the overall mortality in the operative removal of known pheochromocytomas of 0-3%, if the patient is appropriately treated pre-operatively. (2)

Pre-operative assessment should aim to evaluate the extent and adequacy of (alpha) adrenergic block and intravascular volume replacement (as the vascular tree dilates).

During induction of anaesthesia and especially during manipulation of the tumour itself, potentially life-threatening swings in blood pressure can be observed. Invasive arterial blood pressure monitoring is therefore recommended. (3)

Intubation should be attempted only when the patient is deemed adequately anaesthetized (deep). (3)

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RENAL DISEASE.

Introduction.

The kidneys are small retroperitoneal organs, but they receive 25% of the cardiac output. They play an important role in homeostasis.

The functions of the kidney are:

- Excretion of the products of metabolism
- Retention of nutrients
- Control of water and electrolyte homeostasis
- Acid base homeostasis
- Bone metabolism
- Erythropoiesis
- Blood pressure control (renin-angiotensin system)

Assessment of renal function.

Many laboratory tests are not affected until 50% of nephrons are destroyed and are late indicators of renal dysfunction.

Laboratory tests that reflect glomerular filtration rate (GFR)

The normal GRF is 125ml/min.

Urea levels vary with GFR, but are also influenced by dietary protein intake, other diseases (such as gastrointestinal haemorrhage), and intravascular fluid status (dehydration increases urea concentration). Very high urea levels will almost always represent a reduction in GFR.

Creatinine levels in the serum can be used as an estimate of GFR. The normal level in women is 0.6-1.0 mg/dl in women and 0.8 to 1.3 mg/dl in men. Increased muscle mass in men accounts for this difference. In the elderly, who have a reduced muscle mass, mild increases in serum creatinine can indicate significant renal disease. The serum creatinine is slow to reflect acute changes in renal function and may take several days to rise with an acute drop in GFR.

Creatinine clearance is a more reliable measure of GFR. It requires the collection of urine over several hours and a measurement of serum and urinary creatinine.

Tests that reflect tubular function

The renal tubules are responsible for the concentration of urine. Dysfunction is established by demonstrating that the kidneys do not appropriately concentrate urine.

Urine specific gravity over 1.018 demonstrates that there is normal concentrating ability. (Provided there has been no diuretic use or glycosuria).

Urine osmolality can range from 38-1400 mOsm/l in the normal subject.

Urinary sodium excretion should be less than 40 mEq/l. The normal kidney conserves sodium but renal failure or diuretic use will cause a loss of sodium in the urine.

Chronic renal failure (CRF).

CRF is a progressive irreversible deterioration of renal function. End stage renal failure (ESRF) is the result and this requires treatment with dialysis (peritoneal or haemodialysis) or renal transplant to support life.

The mortality of ESRF is high. In the United Kingdom, the 4-year survival for patients with ESRF is only 48%.

CRF is asymptomatic until renal function is reduced to less than 10%. The relationship between serum creatinine and GFR is not linear and serum creatinine will not rise until the GFR has fallen to below 50%. (9)

The commonest causes in the developed world are hypertension and diabetes. Worldwide, the main cause of end stage renal disease is glomerulonephritis, with infections being the predominant precipitants. IgA nephropathy is common in Asia and Pacific regions. (9) Interstitial nephritis can be secondary to renal stones, obstruction of the urinary tract, tuberculosis or nephrotoxins, and accounts for up to 20% of ESRF.

The manifestations of chronic renal failure include:

1. Electrolyte imbalance, which is common, particularly hyperkalemia. Some medications may precipitate hyperkalemia. They include beta-blockers, potassium sparing diuretics such as spironolactone, angiotensin converting enzyme inhibitors or agonists, non-steroidal anti inflammatory agents and other nephrotoxins like aminoglycoside antibiotics. In acute acidosis, potassium moves out of the cells to raise the serum potassium by 0.5 mmol/l for each 0.1 decrease in pH.

Most patients exhibit a mild degree of sodium and water retention but are unable to concentrate their urine in response to acute dehydration.

Magnesium excretion is reduced and serum levels will be elevated, which can lead to muscle weakness, and a potentiation of neuromuscular blockade.

2. Chronic metabolic acidosis occurs in CRF, as there is an inability to secrete hydrogen ions or buffers such as phosphate, or to regenerate bicarbonate. Organic anions are retained in the body and this enhances the fall in bicarbonate levels. (9)

3. Unpredictable intravascular fluid status is common, with the risk of pulmonary oedema and pleural effusions if there is fluid overload. The best treatment is by fluid removal with diuretics or dialysis.

4. Chronic anaemia is common. It results in an increased cardiac output and shifts the oxyhemoglobin dissociation curve to the right to facilitate oxygen delivery to the tissues. The anaemia is normochromic, normocytic and results from decreased erythropoietin levels and reduction in cell life secondary to uraemic toxins. It is best treated with erythropoietin.

5. Platelet dysfunction occurs secondary to uraemia, which can lead to a bleeding tendency. It may temporarily improve with the administration of DDAVP. Blood vessels become fragile, leading to increased bleeding.

6. In the gut, uraemia will cause anorexia, nausea and vomiting, bleeding from stress ulceration, diarrhoea and hiccoughs. The nutritional state of the patient with chronic renal failure is commonly poor, which will lead to poor wound healing. (8)

7. Neurologic changes include, malaise, fatigue, decreased mental ability and encephalopathy with eventual coma. Severe uraemia, fluid and electrolyte imbalance can cause convulsions. A glove and stocking sensory loss progressing later to motor changes can occur. Dialysis and transplantation can improve this neuropathy.

8. Cardiovascular changes, including systemic hypertension, ischaemic heart disease (frequent cause of mortality), cardiac failure and pericarditis. Hypertension may be primary, secondary to salt and water retention or to excess renin production. The incidence of hypertension is nearly 80% in patients with CRF. Fluid overload is treated with dialysis but drug treatment of hypertension may still be required. Pericarditis occurs with uraemia. Sudden death can occur from acute cardiac arrhythmias secondary to ischaemic heart disease and electrolyte abnormalities. (9)

9. Calcium metabolism is altered due to the decline in renal production of calcitriol. The low calcitriol levels decrease intestinal absorption of calcium leading to low plasma calcium. Hyperphosphatemia occurs as the GFR falls and causes a deposition of calcium phosphate in the tissues to lower calcium further. The high phosphate and low calcium levels act to stimulate parathyroid hormone secretion. Hyperparathyroidism leads to demineralisation of bone and fractures.

10. Other endocrine disturbances include impaired glucose metabolism, but a reduced requirement for exogenous insulin in diabetics due to reduced metabolism of insulin in the kidneys. Patients with CRF have a tendency to hypothermia due to changes in temperature regulation and a reduced metabolic rate, as well as heat losses during haemodialysis. (9)

Treatment of chronic renal failure.

The treatment of chronic renal failure is by fluid restriction, diet and avoidance of precipitating factors that will cause further deterioration in function. Ultimately, dialysis will be required. Some patients are on immunosuppressant medications to treat the primary cause of renal failure.

Haemodialysis requires anticoagulation, vascular access (an arterio-venous fistula or vascath), and thrice weekly access to a haemodialysis machine. Large fluid shifts and hemodynamic changes occur during dialysis, which may cause stress on the cardiovascular system. Dialysis will affect the clearance of some drugs. It is recommended that dialysis should be continued until theatre in those receiving peritoneal dialysis, and those having haemodialysis undergo dialysis with minimal heparinisation up to 12 hours prior to surgery. A minimum period of 4-6 hours should ideally

elapse before surgery after dialysis to allow fluid compartment equilibration and clearance of residual heparin and avoid hemodynamic instability. (9)

Peritoneal dialysis is a form of continuous renal replacement therapy (CRRT) and the peritoneum is used as the semi-permeable membrane. Dialysate is instilled via a catheter in the abdominal wall and dwells in the peritoneum for several hours. Fluid removal is achieved by using glucose in the dialysate fluid. (4) If the patient becomes critically ill, peritoneal dialysis may be inefficient due to reduction in intestinal blood flow and hemodynamic instability. The disadvantages of peritoneal dialysis are a reduction in diaphragmatic excursion and the risk of developing peritonitis.

Anaesthetic management.

Thorough preoperative assessment will detect the presence of complications of renal disease. The volume status needs to be determined. Many patients with ESRF on dialysis will know what their ideal weight is, so hypo or hypervolaemia is easier to detect. Sodium and water excretion is relatively fixed and often reduced. The kidneys will have trouble excreting a large fluid load and will be put at further risk with dehydration, as they will have trouble conserving body water. The patient should be normovolaemic prior to surgery and fluid resuscitation is achieved with normal saline or blood when indicated. (8)

Electrolyte and acid base status should be determined preoperatively. The most common abnormalities are hyperkalaemia and acidosis. The presence of hyperkalaemia presents a significant problem. Hyperkalaemia is defined as serum potassium of over 5 mmol/l. The ECG changes occur at a potassium of 6-7 mmol/l and immediate treatment is required if it is over 7 mmol/l. Ventricular fibrillation may occur at concentrations over 10 mmol/l. (8) The use of suxamethonium is contraindicated in the presence of high serum potassium, as a dose of suxamethonium can raise the serum potassium by 0.5 mmol/L, pushing the potassium up even further. High serum potassium can be treated with calcium gluconate (0.5 ml/kg up to 20ml of a 10% solution), 50 ml of 50% glucose (with or without 5-10 units of insulin depending on the presence of diabetes), sodium bicarbonate (1-2 mmol/kg over 5-10 minutes) or nebulised salbutamol. Total body potassium is reduced with dialysis, calcium resonium or a low potassium diet. Other electrolyte abnormalities include, hypo or hypernatremia, hyperphosphatemia, hypocalcemia and hypokalemia. Hypercarbia should be avoided as acidosis shifts potassium out of the cells.

Acidosis is treated with dialysis. Sodium bicarbonate may be used if the pH is less than 7.2 but the side effects are sodium and fluid overload.

The indications for preoperative haemodialysis are hyperkalemia (>6mmol/l), fluid overload and pulmonary oedema, metabolic acidosis and uraemic toxicity. (9)

Vascular access may be challenging due to the fragility of vessels, and the need to preserve potential arterio-venous fistula sites such as the forearm and cubital fossa.

The excretion of water-soluble drugs and their active metabolites is impaired in chronic renal failure. Their half-life is increased and dialysis may not remove drugs or their metabolites. The volume of distribution of drugs is usually decreased, but may be increased if there is fluid retention. Hypoalbuminaemia and acidosis increases the free drug fraction of highly protein bound drugs.

Induction agents undergo redistribution, which accounts for the termination of their effect. They have the potential to reduce cardiac output. The dose of thiopentone may need to be reduced by 30-50%. The pharmacodynamics of propofol is not changed, but the change in volume of distribution and mental state of the CRF patient means that a reduction in dosage is required. (9)

The use of inhalation agents is generally safe. The kidneys are unable to excrete large amounts of fluoride ion, which is potentially nephrotoxic, so it is advisable to avoid the use of enflurane, methoxyflurane and sevoflurane, particularly at low flow rates. Nitrous oxide has no effect on the kidney.

Renal disease slows the excretion of vecuronium and rocuronium. The clearance of mivacurium, atracurium and cisatracurium is independent of the kidney, but the metabolite, laudanosine (produced from the metabolism of atracurium) may accumulate and cause seizures. Gallamine is dependent on renal excretion and should be avoided.

The dose of neuromuscular blockers is reduced and when possible, neuromuscular monitoring should be used. Reversal with neostigmine and either atropine or glycopyrrolate is recommended. The excretion of neostigmine is delayed as it depends on the kidneys, but this does not have any clinical effect. Reversal may be incomplete and it may be necessary to delay emergence from anaesthesia until neuromuscular function is normal. There has been a case report of the use of sugammadex for the reversal of vecuronium in a patient with renal failure and residual neuromuscular paralysis. Sugammadex is a synthetic gamma cyclodextrin that selectively encapsulates steroid-based non-depolarizers and is being studied as rapid reversal agent for rocuronium. The presence of acidosis and electrolyte imbalance will prolong neuromuscular blockade and should be treated appropriately.

In addition to standard intra-operative monitoring, special attention should be paid to the volume status of the patient. Fluid management may require insertion of a central venous catheter and monitoring of central venous pressure for procedures associated with large fluid shifts.

Postoperatively, it is recommended that oxygen be administered for 24-48 hours, particularly after major abdominal or thoracic surgery.

Postoperative management of pain needs to be carefully considered. Regional anaesthesia is effective, but local anaesthetic toxicity can occur due to reduced clearance of the agents and a reduction in the seizure threshold in the uraemic patient. Levobupivacaine is probably safer than bupivacaine because of its higher therapeutic ratio. The presence of a coagulopathy due to uraemic platelet dysfunction or recent heparinisation for haemodialysis is a contraindication to neuraxial blockade and the insertion of a block in a non-compressible site.

Opioids are metabolised in the liver and the metabolites are then excreted via the kidneys. Morphine's metabolite morphine-6-glucuronide is a potential respiratory depressant, and will accumulate in the plasma in renal failure. It has been associated with delayed sedation. The other metabolite of morphine metabolism is morphine-3-glucuronide and it will also accumulate in renal failure. It is associated with antinociception and irritability. Oral doses of morphine will produce higher plasma levels of its metabolites. Morphine and its metabolites are removed during haemofiltration and haemodialysis, but not by peritoneal dialysis. The use of morphine in renal failure appears to be safe provided it is carefully titrated to effect and not given in large doses (as might be required for acute pain).

Norpethidine is a metabolite of pethidine (meperidine) and is normally excreted via the kidneys. In patients with normal renal function, 20 percent of patients will experience toxicity if doses exceed 10 mg/kg/day or therapy is over three days in duration. Its half-life is prolonged from 21 hours to 35 hours in renal failure and its accumulation will result in seizures. A single dose of pethidine in a patient with renal failure is not likely to produce toxicity.

Fentanyl, alfentanil, sufentanil, remifentanil and buprenorphine are potential alternatives, but may need a reduction in dosage. Alfentanil protein binding is altered by renal disease. Its unbound fraction is increased but its clearance is not altered. There may be a decreased dose requirement, but there will be no need to change the frequency of administration. Fentanyl has a high hepatic extraction ratio, with decreased clearance in the presence of uraemia due to alterations in hepatic blood flow. Fentanyl has no active metabolites, but a reduction in dosage is recommended for the acutely unwell (uraemic) patient with CRF. The doses recommended are $\frac{1}{2}$ to $\frac{1}{3}$ of the usual commencement dose. Remifentanil is metabolised rapidly by esterases to a minimally active metabolite, but its administration requires a reliable infusion device and close monitoring, so it is only appropriate in the high dependency setting.

Tramadol is metabolised in the liver, and its metabolites are then excreted in the urine. The manufacturer recommends that the dosage intervals be increased in the presence of a creatinine clearance of less than 30 ml/min and that it be avoided when the creatinine clearance is less than 10 ml/min. This is not practical for treating acute pain.

10% of codeine is metabolised to morphine, which provides most of its clinical effect, the remainder of the dose of codeine is metabolised to codeine-6-glucuronide, which is then excreted by the kidneys. Codeine may cause CNS excitation and seizures at increased doses. It has been reported to cause prolonged sedation in the presence of renal failure.

Non-steroidal anti-inflammatory drugs (NSAIDs) have the potential to worsen renal function due to inhibition of prostaglandin production and afferent arteriolar vasoconstriction in the kidney, which reduces the glomerular filtration rate. NSAIDs reduce creatinine clearance, sodium output and potassium output. (11) The potential for producing acute renal failure is increased in the presence of dehydration, hypotension, pre-existing renal disease, liver cirrhosis and excessive dosage. Ketorolac is extensively metabolised by the liver before being excreted by the kidneys. In the presence of mild renal impairment, the half-life is doubled. (5) The newer COX-2 specific inhibitors such as parecoxib and celecoxib have similar renal side effects. If there is no alternative to NSAIDs or COX-2 inhibitors, then dosages must be kept to a minimum with prevention of hypotension and hypovolaemia and monitoring of renal function. (Creatinine clearance)

Paracetamol is associated with less risk of renal failure than the NSAIDs and is the simple analgesic of choice in the presence of renal failure. It may accumulate in the presence of uraemia, so the dose should be limited to 40mg/kg/day and liver function monitored.

Ketamine is metabolised by the liver and less than 10% is removed during haemodialysis or filtration. It appears to be safe to use as a low dose infusion (at rates between 0.06 and 0.24 mg/kg/hr) such as those used for acute pain management.

Acute renal failure.

Acute renal failure is defined as an abrupt and sustained decline in glomerular filtration rate, which leads to an accumulation of nitrogenous waste products and urea. The incidence ranges from 5-15% in the critically ill patients. (3)

The diagnosis of acute renal failure is made when the urine output is persistently less than 0.5 ml/kg/hour or the serum creatinine rises. (8)

The aetiology of acute renal failure can be classified into pre-renal, renal and post-renal failure. Where pre-renal failure refers to a reduction in renal blood flow and therefore a reduction in glomerular filtration. The normal response of a kidney to hypovolaemia is to conserve water and sodium and to reduce the production of urine. Dehydration, hypovolaemia and hypotension trigger osmoreceptor, volume receptor and baroreceptor reflexes that involve the sympatho-adrenal and renin-angiotensin systems, aldosterone and antidiuretic hormone. The ultimate effect is to produce oliguria with high osmolality and low urine sodium. When normal renal perfusion is restored, urine output recovers. The exception is in sepsis and liver failure, where oliguria is resistant to fluid replacement. (7)

Intra-renal causes of acute renal failure are vascular, glomerular, interstitial and tubular. In the critical care population, acute tubular necrosis (ATN) is the most common cause of acute renal failure. Ischaemia or toxic processes can cause ATN, with sepsis being the most common cause in intensive care patients. (10)

Post renal causes are due to obstruction of urinary outflow and can occur anywhere along the urinary tract. An abrupt cessation of urine flow should prompt an examination of the urinary catheter to ensure there is no obstruction. Even partial ongoing obstruction can lead to renal injury. (7)

The patients at risk for acute renal failure are the elderly, those with exposure to renal toxins (such as non-steroids anti-inflammatory drugs and aminoglycosides), and those with pre-existing renal impairment, postoperative vascular patients, major trauma and septic patients.

There is a high mortality associated with acute renal failure (10-15% and up to 50-90% in the patients with multiple organ dysfunction). Therefore protection of the kidney during any insult is recommended. Renal protection can be achieved with maintenance of perfusion, maintenance of euvolemia and the avoidance of added insults (drugs, intravenous contrast, hypovolemia,

hypoxemia and low cardiac output). Other suggested therapies include diuretics, vasoactive agents, antioxidants and renal replacement therapy. (10)

The use of fluids is especially important in those patients with haemolysis or rhabdomyolysis, where it flushes out casts from the tubules. Renal replacement therapy will remove a significant amount of myoglobin and may be ultimately required for those with rhabdomyolysis. Fluids are also recommended for the patients who have had radio-contrast agents and are at risk for renal failure. The best type of fluid is not known, but normal saline is most commonly used. The use of iso-osmotic non-ionic contrast seems to produce less nephrotoxicity, especially in diabetics undergoing angiography. (3) Fluids are given to restore normovolaemia. Hydration can be guided by the use of central venous pressure monitoring. The aim is to restore urine flow to over 1ml/kg/hr. (8)

Perfusion to the kidney is restored in low cardiac output states with the use of vasoactive drugs to maintain an adequate mean arterial blood pressure. (8)

There is little evidence for the use of medications to protect the kidney from an anticipated insult except for the use of mannitol prior to the administration of intravenous contrast.

The agents that have been tried for renal protection include mannitol, loop and thiazide diuretics and low dose dopamine infusion. Loop diuretics will theoretically paralyse tubular function and therefore reduce oxygen consumption. There is conflicting evidence for their use for renal protection and they have the potential to worsen hypovolemia. In the patient who is oliguric despite adequate hydration and blood pressure, a furosemide infusion may be considered to restore urine flow. (8)

The theory behind the use of dopamine is its action on the dopamine receptors to increase splanchnic and renal perfusion. There is currently no evidence to support the use of low dose dopamine to prevent acute renal failure and it may worsen renal perfusion in the critically ill. (3,10) Fenoldopam is a selective dopamine-1 agonist and increases renal blood flow. Its role in the prevention and treatment of ARF is promising. (10)

N-acetylcysteine (NAC) (with hydration) has been evaluated for the prevention of renal failure after contrast administration and the initial results have been favourable. NAC is an antioxidant and has a positive effect on renal blood flow and GFR in an ischaemic model of ARF. (10) It is not expensive and may be useful for the very high-risk patient.

Renal replacement therapy (RRT) will be required for the treatment of those with severe acute renal failure (and those with end stage renal failure). Patients who require RRT have a mortality of about 50%. (10) RRT assumes all or part of the blood purification and water and electrolyte balance functions of the kidney. It can take the form of peritoneal or haemodialysis. (4) Dialysis differs from ultrafiltration. Dialysis refers to diffusion, that is, movement of solutes along an electrochemical gradient from a compartment with high concentrations to a compartment with low concentrations of solute. An electrolyte solution runs in a counter-current direction to the patient's blood on the opposite side of a semi-permeable membrane. This removes small molecules such as

urea but is less effective for larger molecules. Ultrafiltration is convection. Solute is carried across a semi-permeable membrane in response to a transmembrane driving pressure (solvent drag). This removes fluid and middle-sized molecules. (4)

The indications for the initiation of renal replacement are uncompensated metabolic acidosis ($\text{pH} < 7.1$), severe hyperkalemia ($\text{K} > 6.5$ or rapidly rising and not controlled with medical therapy), symptomatic uraemia ($> 35 \text{mmol/L}$) and fluid overload unresponsive to diuretics. Overdose with a dialyzable toxin such as lithium, salicylates or sodium valproate, severe hyperthermia (over 40 degrees C) and severe electrolyte disturbances ($\text{Na} < 110$ or $> 160 \text{mmol/L}$) are also indications for renal replacement therapy.

In the intensive care setting, continuous renal replacement therapy is used rather than intermittent haemodialysis. CRRT slowly corrects physiologic derangements. An extracorporeal circuit is used to carry the patient's blood through a filter where varying degrees of dialysis and ultrafiltration occur. The blood flow rates are lower than in intermittent haemodialysis. Vascular access is usually a large bore, venous catheter with two ports. Modern machines have a mechanical pump, which replaces the need for an arterial driving pressure in the circuits. (4)

The use of biocompatible synthetic dialysis membranes instead of cuprophane appears to improve overall outcome. High dose continuous replacement therapy appears to be better than lower doses for reducing mortality. Whether or not intermittent haemodialysis is better than continuous renal replacement therapy is not clear. There are theoretical advantages to the use of continuous therapy over intermittent dialysis, particularly with respect to hemodynamic consequences, as intermittent haemodialysis required higher blood flow rates. In the patient with intracranial hypertension, continuous therapy is recommended over intermittent dialysis, as over rapid solute clearance may cause cerebral oedema. The advantages of intermittent haemodialysis are the superior solute clearance, more rapid removal of dialyzable toxins; shorter sessions and less episodes of filter clotting. Any renal replacement therapy that utilizes an extracorporeal circuit will require the patient to be anticoagulated as the circuit will activate the coagulation cascade. In the patient at high risk for bleeding, heparinization of the circuit only is an option. The timing of the commencement of renal replacement to improve outcome is not clear. The early (or late) commencement of dialysis or filtration does not seem to improve outcome. (3)

Monitoring of the patient in acute renal failure should include urine output monitoring with the use of a urinary catheter and drainage system, central venous pressure, blood pressure, electrolytes including potassium, sodium and bicarbonate, and acid base status. It is recommended that urea and/or creatinine levels are measured twice a day. (8)

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ANAESTHESIA FOR THE PATIENT WITH LIVER DISEASE

The liver is one of the largest internal organs of the body. It weighs about one to one and a half kilograms, which amounts to approximately 1.5-2% of lean body mass. It receives a dual blood supply. 20% is oxygenated blood from the hepatic artery and 80% is nutrient-rich blood from the portal vein. The majority of the cells in the liver are hepatocytes, which perform synthetic functions (proteins), produce bile and its carriers, regulate nutrients and metabolise and conjugate lipophilic compounds (such as bilirubin and drugs). The hepatocytes make up two thirds of all cells in the liver and the remaining cells are Kupffer cells (reticuloendothelial system), fat storing cells, endothelial cells, blood vessels, bile duct cells and supporting tissue. (2)

Functions of the liver.

Conjugation of bilirubin

Bilirubin is produced from the degradation of haemoglobin and is made water-soluble by conjugation in the liver. The conjugated bilirubin is then excreted into the bile ducts. Bile salts are produced by the liver and are required for the absorption of the fat-soluble vitamins A, D, E and K. Vitamin K is essential for the production of some of the coagulation factors. (Factor II, VII, IX and X.) (5)

Protein synthesis and metabolism

The hepatocytes synthesise albumin, carrier proteins, coagulation factors and many hormonal and growth factors. Indeed, the liver produces all proteins except gamma globulins and anti haemophilic factor.

Albumin is important for the maintenance of colloid oncotic pressure and binds many drugs. Increased drug sensitivity is not usually clinically relevant until the albumin level drops below 2.5 g/dl. (3) The elimination half-life of albumin is 14-21 days, so a drop in albumin may not be seen in acute liver dysfunction.

The clotting factors V, VII, IX, X, prothrombin and fibrinogen are synthesized by the liver. Only 20-30% of normal levels of these clotting factors are required to stop bleeding. Significant liver dysfunction must be present before bleeding problems occur. The plasma half-lives of clotting factors is in the order of hours, so acute liver failure can lead to a coagulopathy.

The liver also synthesises anticoagulant factors and is responsible for the clearance of activated clotting factors and tissue plasminogen activator. The liver deaminates amino acids and forms urea. (3)

Lipid metabolism

The liver performs beta-oxidation of fatty acids and forms lipoproteins. It also has a role in cholesterol metabolism as it synthesises cholesterol and triglycerides.

Carbohydrate metabolism

Gluconeogenesis and glycolysis occur in the liver and there is a store of glycogen in the liver, which can be broken down by glycogenolysis to supply glucose to the body. The liver normally stores about 75 grams of glycogen that can be depleted by 1-2 days of starvation. The patient with liver disease may have low glycogen stores and may be prone to hypoglycaemia. (3)

Biotransformation of drugs

Drugs that are metabolised by the liver undergo oxidative reactions by the hepatic microsomal systems or are conjugated to make them more water-soluble so they can then be excreted either in the urine or bile.

Liver function tests and assessment of hepatic function.

The traditional tests of liver function measure enzymes that indicate hepatocellular damage or obstruction or the synthetic functions of the liver. These are 'static' tests. New tests are being used to measure the 'dynamic' function of the liver. These include assessment of the formation of metabolites such as monoethylglycine xylidide from lignocaine and the clearance of the anionic dye indocyanine green. (1)

The measurement of the liver enzymes and bilirubin are the most common initial tests. Serum alanine and aspartate aminotransferases (ALT and AST) are elevated in hepatocellular injury, but are not specific. Alkaline phosphatase (ALP) is elevated in obstructive disease but is also released from other tissues and the gamma-glutamyl transpeptidase (GGT) is also elevated in obstruction. Bilirubin levels are elevated in liver disease and may be conjugated (indicating an obstructive pattern) or unconjugated (indicating a failure of the hepatocytes to conjugate it).

The standard tests to assess the synthetic functions of the liver include the measurement of albumin and prothrombin time.

Viral serology will indicate the type of viral hepatitis involved when relevant.

The gold standard in the evaluation of liver disease is a liver biopsy, but is needed less for diagnosis and is used mainly for grading and staging of the disease. (2) A thorough history and examination, laboratory testing and radiological investigations (predominantly ultrasound and computer tomography) will enable accurate diagnosis in most instances.

Types of liver disease.

There are many causes of liver disease, but they generally present in one of few distinct patterns, that is, hepatocellular, cholestatic (obstructive) or mixed. (2) The more common causes of acute liver diseases are viral hepatitis (A, B, C, D or E and mononucleosis, herpes or adenovirus), alcoholic liver disease, drug induced liver disease and cholangitis. The most common causes of chronic liver diseases are chronic hepatitis C, alcoholic liver disease, non-alcoholic fatty liver, chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease. (2)

Hepatocellular

Hepatocellular liver disease such as that caused by viral hepatitis or alcoholic liver disease has features of liver injury, inflammation and necrosis. (2) Liver function testing reveals increased levels of serum alanine and aspartate aminotransferases (ALT and AST) as these are released from damaged hepatocytes.

Obstruction of hepatobiliary tree

Obstructive, or cholestatic liver disease such as that caused by gallstones, malignancy or primary biliary disease produces features of inhibition of bile flow. (2) On liver function testing, there is a raised bilirubin (conjugated), increased gamma-glutamyl transpeptidase and alkaline phosphatase. Ultrasound and computerised tomography have a high sensitivity for detecting bile duct dilatation. (2)

Clinical manifestations of liver disease.

The typical presenting symptoms of liver disease are fatigue, jaundice, itching, right upper quadrant pain, abdominal distension and intestinal bleeding. Some patients have no symptoms but are diagnosed with liver disease on routine blood testing. The patients are then evaluated for the type (hepatocellular or cholestatic) and cause of the disease, grade of the disease (that is, the severity or activity of the disease) and stage of the disease (acute, chronic, early, late, pre-cirrhotic, cirrhotic or end stage). (2)

Fatigue is the most common symptom of liver disease, but is not specific. It is often intermittent and variable in severity. Nausea occurs in more severe disease and pain is most commonly a dull ache in the right upper quadrant unless there are gallstones, which can cause severe pain. Severe pain can also be a feature of liver abscess or veno-occlusive disease. Itching occurs early in obstructive jaundice and later in hepatocellular disease. Jaundice is the most reliable marker of severity of the liver disease. (2) There is usually a darkening of the urine before scleral icterus becomes apparent (with a bilirubin level of over 43 micromol/l or 2.5 mg/dl). In severe cholestatic disease, there are pale stools and steatorrhea. Jaundice with dark urine occurs with unconjugated hyperbilirubinemia such as with haemolysis and the congenital disorders of bilirubin conjugation.

Physical examination is normal in many patients unless the disease is acute or severe and advanced. Examination will focus on signs of hepatic failure, portal hypertension and liver decompensation. Typical physical findings in liver disease are jaundice, hepatomegaly, hepatic tenderness, splenomegaly, spider naevi, palmar erythema and excoriations. The signs of advanced disease include muscle wasting, ascites, oedema, dilated abdominal veins, hepatic fetor, flap, mental confusion and depressed conscious state. Some males with cirrhosis have gynecomastia and testicular atrophy. (2)

Cirrhosis.

Cirrhosis results from a destruction of the architecture of the liver by fibrosis and can occur as a result of any chronic disease of the liver including alcoholism, chronic active hepatitis, primary biliary cirrhosis, haemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency. In the early stages, it is only detectable by liver biopsy. The end result of cirrhosis is an increased resistance to blood flow through the portal venous system. The reduction in portal blood flow is compensated for by an increase in hepatic arterial blood flow. The complications of cirrhosis include varices, ascites, hyperdynamic circulation, cardiomyopathy, anaemia, coagulopathy, hypoxaemia, hypoglycaemia and encephalopathy. Patients with advanced cirrhosis should be screened for oesophageal varices and hepatocellular carcinoma.

The Child-Pugh classification is a staging system for those with cirrhosis. It is based on score derived from levels of serum bilirubin, albumin, prothrombin time, the presence of ascites and hepatic encephalopathy. It was initially devised to stratify patients into risk groups prior to undergoing portal decompression and is a reasonable predictor of survival in many liver diseases and of the likelihood of major complications such as variceal bleeding or spontaneous bacterial peritonitis. (2)

Gastroesophageal varices form due to portal hypertension. These varices may cause severe haemorrhage. They are treated with injection with a sclerosing agent at gastroscopy and some patients are put on beta-blocker therapy. Other treatment includes the infusion of a splanchnic vasopressor such as octreotide. The placement of a nasogastric tube may theoretically induce variceal bleeding, but this is not borne out in clinical practice.

Gastric ulceration can occur in those with liver disease secondary to high portal pressures and reduction in the production of the normal protective mucosal coating of the stomach.

Liver failure.

Liver failure may occur de novo or in the presence of pre-existing liver disease. The liver has the potential to regenerate, but acute liver failure carries a high mortality and the options for treatment are limited. Quality of life is best when recovery or regeneration of the liver occurs after a period of conservative therapy. Liver transplantation is the treatment of choice for fulminant, acute and subacute liver failure.

The overall mortality of acute liver failure without transplantation is up to 90-97%. Unfortunately, some patients may not be suitable for transplantation. There are emerging techniques for the extracorporeal support of the failing liver. (1) These techniques are currently used as "bridging techniques" until liver transplantation.

Liver failure may occur in pregnancy and may be due to acute fatty liver of pregnancy or due to viral hepatitis. When liver failure occurs in this setting, the mortality is up to 60% for the mother. Fetal mortality is also high. (4)

Hepatic encephalopathy, cerebral oedema and hepatorenal syndrome, susceptibility to infection and ultimately multiple organ failure result from hepatic failure. In the surgical patient with pre-existing liver disease, any loss of hepatocellular mass, impairment of liver perfusion or septic complications may exacerbate liver failure (1)

Hepatic encephalopathy.

The first signs of hepatic encephalopathy are often subtle or non-specific such as a change in sleep pattern or personality, irritability and mental dullness. As it becomes worse, there is confusion, disorientation, a decrease in conscious state and eventually, coma. The physical findings include a tremor or flap and fetor hepaticus (slightly sweet ammoniacal odour). (2)

Hepatic encephalopathy and coma will cause an increase in intracranial pressures in the latter stages, which will influence outcome. There is also an accumulation of toxic metabolites such as ammonia and glutamine and an increase in cerebral blood flow, both of which contribute to the rise in intracranial pressure. (1)

Hepatorenal syndrome.

Hepatorenal syndrome is the impairment of renal function in the presence of advanced liver disease. It affects the arterial circulation and activity of endogenous vasoactive mediator systems. (1) There are two forms of hepatorenal syndrome. One is characterised by a doubling of serum creatinine, or halving of creatinine clearance in less than two weeks, the other is a more insidious rise in serum creatinine over several months. The incidence of hepatorenal syndrome is approximately 15% in patients with chronic liver disease. There is a reduction in glomerular filtration rate with sodium and water retention. The sodium and water retention occurs due to several mediators including antidiuretic hormone, the renin-angiotensin-aldosterone system, prostaglandins and the sympathetic nervous system. Progression of the inappropriate sodium and water retention and release of mediators leads to profound renal vasoconstriction and renal insufficiency. (13)

The syndrome may be worsened by an accumulation of toxins that can no longer be removed by the liver. These toxins then impair renal function.

A diagnosis of hepatorenal syndrome is made on the basis of a reduced creatinine clearance less than 40 ml/min in the absence of pre-renal causes. Plasma expansion and cessation of diuretics does not improve renal function and the acute form carries a high mortality of 60% within two weeks of diagnosis. (1) Vasoconstrictors have been advocated to treat hepatorenal syndrome based on the fact that profound splanchnic vasodilatation results in renal vasoconstriction in hepatorenal syndrome. Vasopressin analogues and noradrenaline combined with plasma expansion can reverse the hemodynamic sequelae that underlie hepatorenal syndrome. (1) (8) However, most patients do not recover completely. The placement of a trans-jugular intrahepatic porto-systemic shunt (TIPS)

can reduce portal pressure and can help in the management of the circulatory dysfunction associated with hepatorenal syndrome. (1)

Treatment is supportive with monitoring of urine output, volume status, arterial pressure and initiation of dialysis. Specific liver support such as albumin dialysis may be attempted. The long acting vasopressin analogue, terlipressin, TIPS and extracorporeal liver support is offered in specialised centres.

Cardiac and pulmonary complications of liver disease.

Cardiac dysfunction may complicate cirrhosis of the liver. There is an impairment of systolic and diastolic function of the heart. This remains silent in most patients unless there is a superimposed illness. There is an effective reduction in blood volume as a result of splanchnic dilatation and an absolute increase in the cardiac output. (A low blood pressure and increased heart rate occur). A hyperdynamic circulation develops in 30-60% of all patients with cirrhosis. (13) This increased cardiac output is not sufficient to meet the demands of organ perfusion.

The assessment of cardiac function in those with severe liver disease may be hampered by the presence of encephalopathy. The most appropriate tests for perfusion abnormalities (coronary artery disease) are perfusion scans and dobutamine stress echocardiography (DSE). DSE also allows for the assessment of ventricular function and valvular disease, and can be used as a screening test for pulmonary hypertension and intrapulmonary shunting. (8)

Lung complications include pleural effusions, reduction in diaphragmatic function if there is gross ascites, secondary pulmonary hypertension in the presence of portal hypertension and the hepatopulmonary syndrome, which causes hypoxia.

Hepatopulmonary syndrome is the diagnosis given to hypoxaemia in the presence of hepatic disease that is thought to be caused by vascular abnormalities in the lungs. (13) These vascular abnormalities include apparent shunting caused by intrapulmonary vasodilatation, true shunting and pulmonary hypertension.

The diffusion of oxygen across capillaries is impaired as there is such large amount of vasodilatation that oxygen does not diffuse into the central stream of blood flowing through the vessels. Paradoxically, the hypoxaemia improves in the supine position and worsens in the upright position. This is due to the diversion of blood away from the bases in the supine position, where there is more vasodilatation. (13) Increasing the inspired oxygen concentration will improve oxygenation. True anatomic shunts are less common and are communication between the portal and pulmonary circulations. They may need to be obliterated to improve oxygenation.

Pulmonary hypertension is a mean pulmonary artery pressure of greater than 25 mmHg. The incidence of portopulmonary hypertension is not common, occurring in less than one percent of those with cirrhosis and portal hypertension. (8) Patients who have portopulmonary hypertension and then go on to liver transplantation have a high mortality, particularly if their mean pulmonary artery pressure is greater than 35mmHg and pulmonary vascular resistance is over 250mmHg.

Unfortunately, pulmonary hypertension may not be recognised until it is advanced or until a pulmonary artery catheter is inserted prior to liver transplantation. (13) (8)

Coagulation.

The coagulopathy associated with liver disease occurs due to an impaired synthesis of the coagulation factors by the liver. With the exception of factor VII, tissue plasminogen activator (tPA) and plasminogen activator inhibitor, the liver produces all of the coagulant and anticoagulants in the body. It is also the site of clearance of tPA and activated coagulation factors. (13) There is a disturbance of both coagulation and anticoagulation, but the balance tends towards bleeding.

In cholestatic disease, the synthesis of the vitamin K dependent factors (II, VII, IX and X) is impaired due to poor absorption of vitamin K, which is fat-soluble and dependant on bile salts.

The administration of vitamin K is not always helpful if liver impairment is severe and plasma may need to be administered. Recombinant factor 7a may be a potential treatment. In those patients with an increased risk of pulmonary oedema, the administration of large volumes of fresh frozen plasma is not desirable and the use of cryoprecipitate may need to be considered, as it is presented in a smaller volume (30ml compared with 180-240ml). Cryoprecipitate has lower concentrations of Factor II, V, VII and IX, compared with FFP. French *et al* found that although FFP administration produces a greater improvement in INR (international normalized ratio) and activate partial thromboplastin time, cryoprecipitate improved the coagulopathy of liver disease. (9)

The use of prothrombin complex concentrates in hepatic disease is not recommended due to the risk of thrombosis or disseminated intravascular coagulation caused by the activated factors II, VII, IX and X present in the concentrates.

A thrombocytopenia can occur in severe liver disease and cirrhosis. There is splenic enlargement with portal hypertension and there may be sequestration of platelets by the spleen. Bone marrow suppression and immune-mediated platelet destruction can contribute to the thrombocytopenia of liver disease.

Risk factors for liver disease.

The major risk factors for liver disease are alcohol use, medications, sexual activity (Hepatitis B), travel, exposure to jaundiced or high risk people (hepatitis A), injecting drug use (Hepatitis C), surgery, blood transfusion (before screening for antibody to hepatitis B core antigen), exposure to needle stick injury and family history.

Alcohol intake is associated with an increased rate of alcoholic liver disease in those who consume more than two drinks per day (in women) and three drinks per day (in men). Cirrhosis occurs when there has been excessive intake for over 10 years.

Familial causes of liver disease include Wilson's disease, hemochromatosis and alpha-1 anti-trypsin deficiency.

Treatment of liver disease.

Treatment is based on treating the cause if this is possible, prevention of progression of the disease or complications and supportive therapy. Abstinence from alcohol, and the avoidance of medications that can worsen liver function is important. It is recommended that patients with liver disease be offered hepatitis A vaccine (and hepatitis B vaccine in those at risk). Influenza and pneumococcal vaccine is encouraged. Those with cirrhosis are offered upper gastrointestinal endoscopy to assess for the presence of varices. If large varices are found, beta-blocker therapy is used to prevent progression and bleeding. Screening for hepatocellular carcinoma may include regular ultrasound examination. (2)

Ascites can potentially cause diaphragmatic dysfunction, a reduction in renal blood flow and may lead to a hydrothorax in those with an anatomic defect in the hemidiaphragm (usually on the right side). The medical management of ascites includes a low salt diet, diuretics (typically spironolactone and frusemide) and repeated paracentesis with colloid volume expansion. In the refractory cases, TIPS is performed. (8)

Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in the treatment of the complications of portal hypertension. It is usually used as a bridging therapy before transplantation. It is indicated for acute variceal bleeding, the prevention of variceal bleeding and ascites. It does not prolong survival without liver transplantation and it may lead to a worsening of liver function and encephalopathy. (8) The placement of a shunt is usually done under radiological control and it has a mortality rate of 1-2%. (8)

Hepatic encephalopathy is treated with a low protein diet (to reduce ammonia production), nonabsorbable disaccharides (lactulose) and nonabsorbable antibiotics (neomycin and metronidazole).

Ultimately, liver transplantation is required for those with end stage liver disease or fulminant liver failure that is not likely to resolve spontaneously.

Anaesthesia.

Risks of anaesthesia

Surgery and anaesthesia have the potential to further impair liver function by their impact on hepatic perfusion or toxicity from drugs administered during the anaesthetic.

Inhalation anaesthetic agents affect carbohydrate metabolism by either enhancing the breakdown of glycogen (ether) or by decreasing the rate of glycogenesis and inhibition of insulin release and tissue effects (halothane). Coupled with the stress response to surgery, which increases glycogenolysis, this leads to elevation in blood glucose levels. (5)

Halothane and ether both inhibit the cytochrome P450 enzyme system so slowing oxidative metabolism of drugs such as fentanyl, ketamine, lignocaine, pancuronium and propranolol.

Halothane has the potential to produce jaundice and severe hepatic damage, particularly after a second halothane anaesthetic. The incidence of halothane hepatitis is thought to be 1:7000-30,000 halothane anaesthetics in adults (less in children). (5) The cause of halothane hepatitis is not clear, but two mechanisms of toxicity are possible. There is a mild, self-limiting form of hepatitis that probably represents inadequate oxygenation of hepatocytes, which is probably not specific to halothane alone. The more severe form has been observed to occur after a second exposure to halothane. Eosinophilia, rash, fever and arthralgia occur, and there have been specific antibodies to liver antigens found in patients with halothane hepatitis. An immunologic cause is therefore postulated. The products of halothane metabolism may react with hepatic microsomal proteins to change these proteins so that they become antigenic. There is a genetic predisposition to this injury. (3) The other volatile agents that are metabolised to oxidative halides such as enflurane and isoflurane theoretically have the potential to cause the same problem. They are not as extensively metabolised as halothane and the number of case reports of hepatitis following their administration is low. The diagnosis of halothane hepatitis is a diagnosis of exclusion, as there are much more common causes of hepatitis that occurs postoperatively, such as viral hepatitis. This should not preclude the anaesthetist from using halothane when it is appropriate. (5)

Hepatic blood flow is reduced under anaesthesia due to a reduction in cardiac output. Most of the intravenous and inhalation anaesthetic agents will reduce cardiac output and intermittent positive pressure ventilation, as well as hypocarbia will further reduce hepatic blood flow.

The opioids have the potential to produce spasm of the sphincter of Oddi, which will increase biliary pressure. This is not a contraindication to their use for analgesia in biliary surgery.

Surgery in patients with active liver disease puts these patients at high risk of further deterioration and should therefore be avoided unless the situation is urgent. If surgery is required, coagulation should be corrected with vitamin K and plasma, and drug dosages should be reduced. The patient with acute liver failure is at risk of over sedation and nitrous oxide may be sufficient for anaesthesia. Intraoperative blood glucose should be maintained. Acidosis, hypoxaemia and electrolyte abnormalities are likely.

There is no ideal anaesthetic technique for patients with acute or chronic liver disease. Perfusion to the liver and oxygenation are the aims during any anaesthetic.

The most likely indication for surgery is biliary obstruction. Obstruction results in conjugated hyperbilirubinemia and can occur secondary to a stone in the common bile duct, pancreatic tumour or ascending cholangitis. Hepatocellular function is largely preserved but may deteriorate if there is prolonged obstruction. The important issues in these patients tend to be related to the presence of jaundice and impaired coagulation due to a decrease in vitamin K dependent coagulation factors. The coagulopathy may need to be corrected and hepatorenal syndrome avoided by adequate hydration and the avoidance of any renal toxins. Importantly, a pneumoperitoneum, as required for laparoscopic cholecystectomy may reduce renal blood flow.

In patients with cirrhosis, the perioperative mortality rate (within 30 days of surgery) was found to be 11.6%, with a complication rate of 30.1% by investigators from the Mayo Clinic. (10) The

most frequent complication was postoperative pneumonia. The factors associated with morbidity and mortality were found to be male gender, a high Child-Pugh score, the presence of ascites, elevated creatinine, chronic obstructive pulmonary disease, perioperative infection, gastrointestinal bleeding, surgery on the respiratory system and intraoperative hypotension. (10)

In the patient undergoing liver resection or partial hepatectomy as a donor, there is a real risk of complications and death. These patients need to be assessed very carefully as impairment of the function of the remaining liver may lead to hepatic failure. A useful test is the disappearance rate or retention of indocyanine green dye after 15 minutes, as this correlates with the number of viable hepatocytes. (14) The liver can regenerate itself to some extent and indeed, the rate of regeneration after resection has been found to be up to 90%, with full functional recovery within one month in previously well donors.

During liver surgery, one of the major risks is blood loss and the requirement for transfusion. If there is no contraindication, then blood salvage may reduce the need for homologous blood transfusion. Intraoperative hypothermia will worsen any blood loss.

Drug metabolism

The metabolism of many drugs will be affected by liver disease. Pseudocholinesterase is synthesised in the liver and is responsible for the metabolism of suxamethonium and mivacurium. Severe liver disease will reduce the pseudocholinesterase level and increase the duration of action of suxamethonium. This tends not to be clinically relevant, as the duration is usually not extended by more than 30 minutes.

Chronic liver disease may lead to decreased drug metabolism due to decreased numbers of enzymes or decreased blood flow. Drugs with high hepatic extraction ratios are most affected by a reduction in blood flow, and those with a low extraction ratio are dependent on enzyme activity and protein binding. Induction agent doses should be titrated to effect and the dose interval between doses of muscle relaxants should be prolonged. Neuromuscular function monitoring is advantageous. Atracurium is a good choice for neuromuscular blockade, as it does not depend on the liver for metabolism or excretion.

Biliary obstruction does not tend to significantly alter drug handling, and normal doses of thiopentone, opioids, benzodiazepines and muscle relaxants are used. (5)

Regional anaesthesia

Amide local anaesthetics are metabolised in the liver and their total dosages may need to be lowered in those with hepatic impairment, as the risk of toxicity is greater. The maximum daily dose of bupivacaine should be halved. (6)

Because liver disease may lead to a coagulopathy, neuraxial anaesthesia is not considered to be safe. The previously well patient undergoing liver resection may also develop a coagulopathy and epidural analgesia is not advised in this situation. (14)

Postoperative pain management

There is very little literature about the safe use of analgesics in the patient with hepatic disease. Most recommendations are made based on the understanding of the metabolism of drugs and their potential toxicity.

In the presence of hepatic impairment, most drugs will have a reduced clearance and increased oral bioavailability. The opioid least subject to an alteration in metabolism is remifentanyl, but it is given via infusion and is only used in the high dependency setting. Tramadol may be given to those with mild hepatic impairment at lower doses (50mg) with longer dose intervals. Methadone is contraindicated and codeine is not recommended. Fentanyl is subject to a high hepatic clearance and a dose reduction is recommended, but it has not been extensively studied in the presence of hepatic impairment. (6) Morphine has the potential to precipitate hepatic encephalopathy, and again, studies in liver failure are absent or not useful. Sufentanil has been used in patients with uncomplicated cirrhosis with no significant reduction in clearance.

Ketamine undergoes mostly hepatic metabolism and there is no data to guide the appropriate use in liver failure. (6)

Anti-epileptics are sometimes considered as an adjunct for the treatment of acute neuropathic pain. Carbamazepine and valproate have the potential to cause fulminant hepatic failure and should be avoided. The safest anti-epileptic in the presence of liver impairment appears to be gabapentin, which undergoes renal excretion. (6)

The non-steroidal anti-inflammatory agents have the potential to elevate liver enzymes and administration in hepatic impairment leads to higher blood levels with the potential to induce renal toxicity. It is recommended that the doses be reduced. (6)

Paracetamol may unpredictably accumulate and lead to hepatic necrosis and acute liver failure. (6, 7) Therapeutic use of paracetamol in chronic alcoholics is reported to be one of the most frequent causes of acute liver failure in the United States. (7) Liver cirrhosis can impair the ability of the liver to conjugate drugs and cause an accumulation of the toxic metabolite of paracetamol that is produced by the alternative metabolic pathway. Drug dosages should be reduced and liver function (and if appropriate, paracetamol levels) be monitored if paracetamol is to be used in cirrhosis. It is recommended that the use of paracetamol in moderate to severe liver failure be avoided altogether. (6)

Paracetamol is metabolised by two pathways in the liver. Most of the dose is conjugated to non-toxic compounds but 5% is metabolised by microsomal enzymes to produce a potentially toxic metabolite (N-acetyl-p-benzoquinonimine, NAPQI), which has a high affinity for glutathione and cysteine to produce a non-toxic metabolite. With high doses of paracetamol, glutathione, which normally deactivates toxic oxygen radicals, and cysteine, which is present in intracellular enzymes, will be depleted, causing hepatocellular death. N-acetylcysteine is given to restore depleted glutathione levels and act as an alternative substrate for NAPQI. (7)

Conclusion.

The liver performs many essential physiologic functions. Hepatic impairment may be acute or chronic and has multiple causes. The predominant abnormalities of liver function are hepatocellular or obstructive. Obstructive disease is a common reason for surgery and anaesthesia for these patients is geared towards the correction of any coagulopathy and avoidance of hepatorenal syndrome. Many liver diseases progress to cirrhosis and result ultimately in portal hypertension. Cirrhosis may not be clinically apparent, but anaesthesia for these patients should focus on preservation of remaining hepatic function. The patient with liver failure will rarely present for surgery except in an emergency or for transplantation. Mortality from acute liver failure is increased, with or without surgery.

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PERI-OPERATIVE RESPIRATORY DISEASE.

Effects of general anaesthesia on the respiratory system.

All general anaesthetic and some regional techniques will affect pulmonary mechanics. The vital capacity is reduced by 25-50% and the residual volume increases by 13%. The expiratory reserve volume decreases by 25% with lower abdominal procedures and 60% after upper abdominal procedures. The tidal volume decreases 20% and functional residual capacity is reduced by one third. Pulmonary compliance is reduced. As a result, atelectasis, hypoventilation, hypoxemia and lung infection can occur. The changes in pulmonary mechanics take up to two weeks to resolve.

Reflex inhibition of phrenic nerve output results in postoperative diaphragmatic dysfunction. At high doses anaesthetics depress the activity of all respiratory muscles. (Warner 2006) There is a lack of respiratory muscle coordination, which reduces efficiency, changes the shape of the chest wall and results in hypoventilation. Anaesthetic agents will cause the development of ventilation to perfusion mismatching and attenuation of hypoxic pulmonary vasoconstriction.

General anaesthesia affects alveolar macrophage function, inhibits mucociliary clearance, increases alveolar-capillary permeability, inhibits surfactant release, and enhances the sensitivity of the pulmonary vasculature to neurohumoral mediators. This can contribute to the development of postoperative pulmonary complications. (Rock and Rich, 2003)

Upper abdominal and thoracic procedures produce a greater effect than peripheral procedures. The respiratory muscles are disrupted by surgery and pain may limit the motion of the respiratory musculature. (Warner 2006). In addition, stimulation of visceral afferent nerves changes the activation of respiratory muscles. In patients undergoing laparotomy, the functional residual capacity decreases to 50% of baseline. Thoracic surgery may increase non-specific airway tone and reactivity, which may lead to bronchospasm and ultimately, pneumonia. Bronchodilators may be useful in these patients, even if there is no asthma or chronic obstructive pulmonary disease (COPD).

Laparoscopic surgery has been advocated for the patient with respiratory disease because there is improved one second forced expiratory volume and forced vital capacity, better oxygenation and improved ventilation compared with open surgery. However, the site of surgery is critical in determining whether diaphragmatic dysfunction will occur. There have been no studies showing a reduction in complications such as pneumonia, bronchitis or respiratory failure in laparoscopic surgery, but there is less pain and faster mobilisation, which may be advantageous.

Postoperative pulmonary complications.

The incidence of serious peri operative respiratory complications has been reported to be 5-10% of patients undergoing surgery and anaesthesia. (Hata JS) The incidence of less serious complications is 30-80%. (Rock and Leavell)

Postoperative pulmonary complications include diaphragmatic dysfunction, ventilation to perfusion inequality, hypoxemia, a reduction in functional residual capacity, hypoventilation and elevated arterial carbon dioxide, atelectasis, lung infection, bronchospasm and ventilatory failure requiring mechanical ventilation.

In the patients who develop pneumonia within 14 days of surgery, there is a mortality rate of 23%. (Hata 2004) For the patient requiring prolonged intubation post operatively, subglottic secretion suctioning may limit aspiration and reduce the rate of pneumonia by 50%. (Hata 2004) The use of epidural analgesia can reduce the incidence of postoperative pneumonia and other pulmonary complications compared with systemic opioid therapy for pain relief.

Postoperative hypoxemia is common. Although diffusion hypoxia may be an early cause of hypoxemia, the most common reasons for postoperative hypoxia are ventilation-perfusion mismatch, atelectasis, hypoventilation or airway secretions. Even small concentrations of volatile anaesthetics blunt the ventilatory response to hypoxemia and hypercarbia, probably by depression of peripheral chemoreceptors. The ventilatory response is least affected by desflurane. Hypoxia may persist for several days postoperatively. It is beneficial to administer oxygen for a few days to those at risk from cardiac events, especially if a laparotomy has been performed.

The risk factors for the development of postoperative pulmonary complications include cigarette smoking, underlying chronic respiratory disease, emergency surgery, prolonged anaesthetic time, advanced age (over 70 years), renal failure, poor nutritional state, significant intraoperative blood loss and those undergoing upper abdominal or thoracic procedures. The risk is 10-40% for those having surgery in the thorax or abdomen. The value of preoperative lung function testing to quantify the risk is not established and in many situations, it is neither possible nor indicated. (Hata 2004)

Interventions that have been used to prevent postoperative pulmonary complications include incentive spirometry, pain relief and bronchodilators but none of these have been entirely effective.

Pulmonary aspiration should be prevented using a combination of strategies including adequate fasting times, rapid sequence induction, the use of regional anaesthesia, and pharmacologic methods such as histamine receptor blockers, proton pump inhibitors, metoclopramide and non-particulate antacids. In the postoperative care of patients, the head of the bed should be elevated. It has been shown that avoiding the supine position can reduce nosocomial pneumonia. (Hata 2004).

Non-invasive positive pressure ventilation can decrease the work of breathing, recruit lung volume, improve lung compliance, reduce hypercarbia and decrease oxygen consumption. It is an effective treatment for acute respiratory failure and acute pulmonary oedema. It can help to avoid reintubation and can be used in the weaning process to allow earlier extubation.

Chronic obstructive pulmonary disease.

Definition.

Chronic obstructive pulmonary disease (COPD) is characterised by poorly reversible airflow limitation. It is a clinical spectrum of diseases including emphysema and chronic bronchitis. It is usually progressive and is associated with an abnormal inflammatory response to noxious particles. The main symptoms of COPD are cough, dyspnoea and wheeze. At least 60% of the risk of COPD is attributable to smoking. (Wilson 2007)

Chronic bronchitis is characterised by the presence of cough, sputum, recurrent infection and airway obstruction that is present for greater than three months per year for over two years. There is mucous gland hyperplasia with mucous plugging, inflammation and oedema, peribronchiolar fibrosis and narrowing of the airways. Bronchoconstriction may also be present.

Emphysema is characterised by the presence of progressive dyspnoea and a cough. There is a progressive destruction of the elastic and collagen network in the lungs without fibrosis, which leads to enlarged air spaces. With the loss of the supporting tissue, there is airway narrowing and collapse.

Over 2.5 million deaths per year are due to COPD worldwide. (WHO 2000) In Australia and the United States, COPD is the fourth most common cause of death after heart disease, cancer and cerebrovascular disease.

Prognosis.

Lung function declines over the long term in COPD sufferers. The prognosis of chronic bronchitis is poor, with death occurring within five years after the first episode of acute respiratory failure. There seems to be a greater decline in lung function in those patients with a greater number of acute exacerbations. Acute exacerbations requiring hospital admission carry a mortality of approximately 26%. (Singh S. Chronic obstructive respiratory disease. Current Anaesthesia and Critical Care 2003; 14:74-80.)

Pathophysiology.

COPD is caused by a combination of genetic and environmental conditions. The most important of these is exposure to cigarette smoke, but the presence of alpha 1 antitrypsin deficiency will also cause COPD secondary to autodigestion of pulmonary tissues by proteases. COPD is more common in men. The estimated number of smokers world wide in 2003 was 1.1 billion.

Inflammation of the airways, airway remodelling and parenchymal destruction lead to airflow limitation. CD8+ lymphocytes, alveolar macrophages and neutrophils are the most frequently isolated cell types from the distal airways. In asthma, the more commonly isolated cells are CD4+ lymphocytes and eosinophils.

There is an irreversible airflow obstruction in COPD that results from fibrosis and narrowing of the airways and a loss of elastic recoil due to the destruction of alveolar supporting tissue that normally maintains the patency of the small airways. By contrast, there is reversible airflow obstruction in asthma that is secondary to an accumulation of inflammatory cells, mucous and plasma exudate in the bronchi and smooth muscle contraction in the airways, with hyperinflation during exercise.

Diagnosis.

COPD presents at a moderately advanced stage, as there is subclinical progression of the disease. The main clinical features are a history of exposure to cigarette smoke, chronic productive cough and shortness of breathe. Spirometry can be used to confirm COPD and to monitor progression of the disease. The forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are measured. The ratio of FEV1: FVC is less than 70% of the predicted value and the FEV1 is less than 80% of the predicted value. Arterial blood gases (ABG) are usually performed in those patients with an FEV1 of less than 40% or with signs of right heart failure.

Lung function testing will reveal an increase in the residual volume and functional residual capacity. The advantage of an increase in the RV and FRC is an increase in the airway diameter. The cost is a greater work of breathing at these higher lung volumes.

Management of COPD.

The goals of management are to assess and monitor the severity of disease, reduce risk factors, to provide symptom relief and to prevent disease progression and the development of complications.

The severity of symptoms and airflow limitation, the frequency and severity of exacerbations, the presence of complications and co-morbidity, the presence of respiratory insufficiency, general health and number of medications required to control symptoms determine severity of COPD.

Where spirometry is available, it can be useful to determine to overall severity of the disease and to assess progression of the disease over time. The British Thoracic society guidelines (1997) classify severity according to FEV1 as a percentage of predicted FEV1 and the symptoms. That is mild COPD is a FEV1 of 60-80% predicted, moderate if FEV1 is 40-59% predicted and severe if FEV1 is less than 40%. The GOLD (Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2006) group has different cut off values for determining the severity of COPD.

Treatment of stable COPD.

Spirometry and reversibility testing are used to assess the progression of the disease and to determine whether there is a response to inhaled bronchodilator or corticosteroid. Over the long term, there should be a stepwise increase in the treatment depending on the symptoms and results of spirometry.

Health education is important. The cessation of smoking is the most effective way of preventing COPD and slowing disease progression. Pulmonary rehabilitation with exercise and strength building will improve the quality of life by reducing dyspnoea and fatigue and increasing exercise capacity. The patient's nutritional state needs to be addressed. Obesity needs to be controlled and malnutrition should be corrected. Prophylactic vaccination against the influenza virus and pneumococcus may help to avoid infective exacerbation of COPD.

Bronchodilators are used to provide symptomatic relief. There is no difference in the effect of ipratropium over beta agonists, but once a day dosing with the longer acting tiotropium has been shown to improve short-term lung function, symptom control and quality of life over standard therapy and placebo. Beta-2 agonists rarely improve expiratory airflow by more than 10% and the anticholinergics are more effective for chronic bronchitis and emphysema than for asthma.

Regular inhaled corticosteroids *may* reduce the rate of exacerbations but are only recommended if there has been a positive response to steroids in spirometric reversibility. They may also be useful in the patients with severe disease with frequent exacerbations to reduce the number of exacerbations.

Long-term oxygen therapy improves survival in patients with chronic respiratory failure and cor pulmonale, but is expensive. It is used in the patients with a PaO₂ less than 60 mmHg, a hematocrit over 55% or evidence of cor pulmonale. The aim is to increase the PaO₂ to between 60 and 80 mmHg. The use of oxygen will improve pulmonary hypertension and heart function. Nocturnal non-invasive positive pressure ventilation may have a place in those patients with symptomatic hypercarbia. Surgery for COPD involves resection of bullae or lung volume reduction and is reserved for the patients with severe emphysema.

Diuretics, oxygen and inotropes are indicated for the patient with cor pulmonale and right heart failure.

Management of an acute exacerbation of COPD.

Exacerbations of COPD occur more frequently with deteriorating lung function. They are caused by infection, air pollution but in up to one third of cases, the cause is not determined.

Oxygenation is maintained with the careful administration of oxygen. Some patients with carbon dioxide retention are dependant on their hypoxic ventilatory drive and are susceptible to ventilation and perfusion mismatching with the administration of oxygen. The amount of oxygen delivered is usually restricted to a level where the arterial oxygen saturation is maintained at about 90-92% but the use of controlled oxygen therapy to achieve a higher paO₂ may be safe as long as the acid-base status of the patient is monitored.

Bronchodilator therapy is useful when there is reversible airway obstruction present. Beta 2 agonists such as salbutamol and anticholinergics such as ipratropium or tiotropium are most commonly used. There is no strong evidence for use of methylxanthines such as aminophylline.

With improvement in the condition, a metered dose inhaler with a spacer can replace a nebulizer for the administration of bronchodilators.

Steroids can be given orally, by injection or inhalation. Treatment with corticosteroids increases the rate of lung function improvement over the first 3 days, reduces the rate of treatment failure and reduces the duration of hospitalisation. However the use of steroids is associated with an increased risk of adverse events.

Antibiotics are not given routinely for an acute exacerbation of COPD unless an infection is present.

Ventilatory failure is treated with either non-invasive positive pressure ventilation via a facemask, or mechanical ventilation. Non-invasive positive pressure ventilation reduces the need for mechanical ventilation and improves survival. The need for mechanical ventilation indicates a worse prognosis. Weaning can be difficult when prolonged ventilation (over 48 hours) is required.

Preparation of the patient with COPD for surgery.

The preoperative history of the patient with COPD will necessarily focus on the presence of symptoms such as dyspnoea, cough and wheeze, as well as the exposure to risk factors, particularly cigarette smoke. A past history of previous hospitalisations (particularly if intubation was required) and a review of current therapy, exercise tolerance, weight loss and evidence of right heart failure will give an indication of the severity of the disease. Previous anaesthetic problems, in particular the need for postoperative intubation, and the presence of a current or recent chest infection may enable quantification of the risk for peri operative pulmonary complications.

Clinical signs of respiratory disease include the breathing pattern, reduction in breath sounds and wheeze on auscultation. An elevated jugular venous pressure, peripheral oedema and the presence of a tricuspid regurgitation murmur indicate right heart failure.

Laboratory investigations that may be useful include; the white cell count (elevation indicates current infection), an increased hematocrit is suggestive of chronic hypoxemia, elevated bicarbonate levels occur when there is respiratory acidosis and hypokalemia occurs with increased use of beta agonists. Treatment of hypokalemia may improve muscle strength.

Arterial blood gases may show hypoxemia or hypercarbia in the patient with severe disease. The 'pink puffer', who is the older cachectic patient with emphysema, has an arterial oxygen tension of over 60mmHg and a normal arterial carbon dioxide tension. The 'blue bloater', who tends to be the patient with chronic bronchitis, will have a paO_2 less than 60mmHg and $paCO_2$ over 45mmHg, with evidence of cor pulmonale.

The chest x-ray is not usually changed much in chronic bronchitis unless there is a current infection. Hyperinflation, bullae and flat diaphragms can be seen in some emphysematous

patients. In an acute exacerbation, there may be atelectasis, pulmonary infiltrates or pneumothorax. The presence of cardiomegaly and cancer are ominous.

Typical ECG findings are a reduced QRS voltage and evidence of right heart strain such as right bundle branch block, right axis deviation, peaked p waves, and arrhythmias, typically atrial fibrillation.

Prevention and reduction of peri operative pulmonary complications centres on the cessation of smoking. Pharmacological treatment should be continued, infections treated preoperatively, and effective hydration and analgesia maintained after surgery. Poor hydration will allow pulmonary secretions to dry out and become inspissated, whereas postoperative pain will prevent coughing, large tidal volumes and early ambulation.

Management of anaesthesia.

Regional anaesthesia is preferred for surgery on the extremities, perineum and lower abdomen. Neuraxial techniques that produce a block higher than the sixth thoracic dermatome may reduce effective coughing due to abdominal muscle weakness and a reduction in expiratory reserve volume. Some brachial plexus techniques will block the phrenic nerve or have the potential to cause a pneumothorax. Postoperative pain management with regional techniques will improve analgesia, allowing the patient to cough after abdominal or thoracic surgery, but the disruption of abdominal musculature from the surgery will also impair the ability to deep breathe and cough. The advantage of using regional techniques is the avoidance of opioid analgesics that can cause respiratory depression. Caution should be exercised if sedation is used to facilitate regional anaesthesia, as it is counterproductive.

Induction of general anaesthesia is achieved with any of the intravenous agents. Agents that cause histamine release are best avoided as they have the potential to cause bronchospasm. Ketamine is a good choice of induction agent, as its sympathomimetic effects will cause bronchodilatation, but its major drawback is its propensity to cause increased cardiac workload and increased pulmonary artery pressures, so care should be exercised in those with cardiac disease or pulmonary hypertension.

After induction, tracheal intubation should only be attempted when there is adequate suppression of airway reflexes. Muscle relaxants facilitate intubation, but those that release histamine should be avoided, such as atracurium, mivacurium or d-tubocurarine. If there is no requirement for tracheal intubation based on surgical or anaesthetic grounds, it is reasonable to hold a facemask or place a supraglottic device such as a laryngeal mask, as this will reduce the stimulus to bronchoconstriction.

The volatile anaesthetic agents have bronchodilator activity and are useful in COPD, as there is minimal postoperative respiratory depression and regional hypoxic pulmonary vasoconstriction is attenuated. Nitrous oxide is more soluble than nitrogen and will rapidly expand any air filled spaces, so should be avoided or used with caution in the presence of large emphysematous bullae or a pneumothorax. It also increases pulmonary artery pressures and pulmonary vascular

resistance, making it potentially hazardous if there is cor pulmonale or pulmonary artery hypertension. All gases should be humidified, or a low fresh gas flow used in order to prevent the drying out of secretions.

Opioids are useful analgesics and can blunt the airway reflexes and deepen anaesthesia. However, they have the potential to cause postoperative respiratory depression. In addition, morphine is well known to release histamine.

Reversal of neuromuscular blockade is essential to allow the patient to breathe following a relaxant general anaesthetic. Neostigmine given on its own will produce a vagal-related bronchoconstriction and bronchorrhea so should be administered with an anticholinergic agent such as atropine or glycopyrrolate.

Mechanical ventilation can be challenging during general anaesthesia. It may not be possible to avoid an increase in arterial carbon dioxide as expiratory time is prolonged and inflation of the lungs during the expiratory phase will cause air trapping, increased airway pressures and reduced venous return. Expiratory time can be increased with the use of larger tidal volumes (10 - 15 ml/kg) and slower respiratory rates.

Extubation at the conclusion of anaesthesia can be achieved in either a light or deep plane. Some anaesthetists prefer to extubate their patients under deep volatile anaesthesia whilst they are spontaneously ventilating in an attempt to avoid bronchospasm. This may not always be possible, as many patients are at risk for regurgitation and aspiration. An attempt to blunt the airway reflexes can be made with the use of inhaled beta agonists or intravenous lignocaine (1.5mg/kg).

Postoperative care.

Postoperative complications include the development of atelectasis, pneumonia, hypoxemia and respiratory failure requiring ventilation.

Adequate analgesia is important to allow for deep breathing and coughing after anaesthesia and surgery. This is usually achieved with either neuraxial blockade or multi-modal analgesia to avoid the administration of large doses of opioids. Complete pain relief does not restore vital capacity or functional residual capacity however. Delayed respiratory depression can occur with neuraxial opioid use, particularly in the elderly, opioid naïve and those receiving systemic opioids as well.

The residual effects of the anaesthetic agents will reduce oxygenation and cause carbon dioxide retention. The longer the duration of surgery, the more likely there will be postoperative pulmonary complications.

Conscious deep breathing will help re-expand the lungs. Chest physiotherapy and incentive spirometry (voluntary deep breathing and holding the inhaled volume to re-expand collapsed alveoli) is useful when it is available. Early ambulation will help to increase the functional residual capacity and improve ventilation to perfusion matching.

The need for postoperative ventilation is determined on an individual patient basis. Those who have a resting arterial carbon dioxide partial pressure of over 50 mmHg, a FEV1 less than one litre, FVC less than 50-70% predicted or FEV1/FVC less than 50% predicted may require postoperative ventilation. The patient who has had upper abdominal or thoracic surgery is at particular risk of postoperative ventilatory failure.

Care should be taken not to correct the arterial carbon dioxide tension too rapidly if there has been chronic CO₂ retention. The kidneys will not be able to excrete the bicarbonate and cardiac arrhythmias or seizures may result. During postoperative ventilation, the recommendation is to aim for p_aO₂ between 60 and 80 mmHg and to keep the CO₂ at a level that will control the pH between 7.35 and 7.45. Typically, the inspired oxygen concentration is set at 50%, tidal volume 10-15ml/kg and respiratory rate 6-10 breaths per minute. Positive end expiratory pressure may be required to improve oxygenation, but it has the potential to cause air trapping.

Asthma.

Definition.

Bronchial asthma is characterized by an increased responsiveness of the airways to various stimuli, reversible airflow obstruction and chronic inflammatory changes in the submucosa of the airways. Airway hyper reactivity is present even when the patient is asymptomatic. The airflow obstruction is reversible.

During an acute asthma attack, the FEV1 is reduced to less than 35% and the FRC increases by as much as 2 litres. The total lung capacity is normal. In mild asthma, the PaO₂ and PaCO₂ are normal, but with worsening obstruction the PaO₂ will drop to less than 60 mmHg and the PaCO₂ will start to rise with increasing fatigue. The FEV1 is less than 25% in a severe attack.

Asthma can be classified according to the underlying pathophysiology and exacerbating factors. In allergen-induced asthma, there is an IgE mediated response to allergens and in the idiosyncratic type; bronchoconstriction results from increased parasympathetic tone. In both types the end result is a release of mediators such as histamine, leukotrienes, prostaglandins, bradykinin, thromboxane and eosinophilic chemotactic factor. These mediators cause severe airway hyper-reactivity and inflammation.

Asthma occurs in 3-5% of adults and 7-10% of children. In children, there is a male preponderance. Allergen-induced asthma tends to occur more commonly if there is a family history of asthma or atopy.

Triggers of asthma include exposure to particular allergens (dust mite, animal dander, pollens), exercise (especially in cold weather), aspirin and food preservatives such as bisulfite and metabisulfite, infection and beta-blockers. The presence of a tracheal tube is a strong stimulus for bronchospasm.

Treatment of asthma.

The regular use of inhaled corticosteroids is recommended in all but the patients with occasional mild asthma. Inhaled beclomethasone is used and is not associated with adrenal suppression, but can contribute to the development of oral candidiasis.

Beta-2 agonists are used as bronchodilators for symptomatic relief of bronchoconstriction or for pre-treatment of exercise-induced asthma. These agents may cause sympathetic nervous system stimulation including tachycardia, hypertension, arrhythmias and an intracellular shift of potassium.

The anticholinergic agents block muscarinic receptors in airway smooth muscle and therefore inhibit vagal cholinergic tone.

Children with asthma may be prescribed cromolyn via a metered dose inhaler. It stabilises mast cell membranes and is used for prophylaxis only. It is ineffective if there is bronchoconstriction.

Theophylline is less commonly used as it has some serious side effects (arrhythmias and seizures) and a narrow therapeutic range.

The emergency treatment of asthma involves the repeated administration of beta-2 agonists, corticosteroids and when there is evidence of carbon dioxide retention and hypoxia, intubation and mechanical ventilation. A general anaesthetic with a volatile agent may be indicated in the patient who is difficult to ventilate.

Preparation of the patient with asthma for surgery.

A thorough preoperative assessment needs to be performed in order to assess the patient for the risks of intra and postoperative pulmonary complications and to determine how well the asthma is controlled.

The risk factors for the development of postoperative pulmonary complications are a recent exacerbation (airway hyper reactivity can persist for several weeks after an episode), the presence of ongoing bronchospasm and a history of tracheal intubation for asthma.

The patient who is asymptomatic and has had no recent episodes of asthma nor requires ongoing medication can undergo anaesthesia and will only require careful observation.

The patient with a history of recurrent asthma and requires ongoing bronchodilator therapy should have their condition optimised even if there are no symptoms present. This may require regular inhaled corticosteroids or oral corticosteroids if there has been a history of moderate to severe asthma with intensive care admission and mechanical ventilation. Bronchodilator therapy should continue.

The symptomatic patient with ongoing bronchospasm should have elective surgery delayed to allow treatment with bronchodilators and corticosteroids. Treatment should be initiated 24-48 hours prior to surgery with 40-60mg of prednisolone daily. There is no evidence to indicate that the use of peri operative steroids for asthma increases wound infection rates. (Rock) Patients who are wheezing should receive intensive bronchodilator therapy.

In emergency surgery, nebulized beta agonists, steroids and possibly adrenaline may be required. Regional anaesthesia is preferable to avoid the need for manipulation of the airway.

Premedication of the asthmatic should involve the continuation of bronchodilator therapy and steroid supplementation in the patient on chronic steroids. An opioid premedication should be avoided as it may lead to ventilatory depression.

Management of anaesthesia.

The goal in the asthmatic undergoing general anaesthesia is to depress the airway reflexes so as to avoid bronchoconstriction in response to mechanical stimulation. Regional anaesthesia is recommended for superficial or extremity surgery, particularly in the poorly controlled asthmatic. However, there has been no measured difference in postoperative pulmonary complication rates between those patients who received general and those who received regional anaesthesia. (Rock)

Induction of general anaesthesia can be achieved with barbiturates, ketamine or propofol or with a volatile agent such as sevoflurane or halothane. Ketamine is a good agent as its sympathomimetic effects cause bronchodilatation. The most common cause of bronchospasm is intubation of the trachea. Therefore, whatever induction agent is used, large doses may be required to block the airway reflexes.

As the volatiles are bronchodilators, they are very useful for the maintenance of general anaesthesia, except desflurane, which causes airway irritation.

The use of opioids for analgesia may be problematic, as they will produce some respiratory depression. Morphine releases histamine, which can cause bronchoconstriction.

The neuromuscular blockers that release histamine are not ideal. Pancuronium and vecuronium are good choices for muscle relaxation. Neuromuscular blockers will improve chest wall compliance, but will not have any effect on smooth muscle airway tone or lung compliance. The prolonged use of neuromuscular blockers in ventilated asthmatics is associated with myopathy.

As in the patient with COPD, the asthmatic patient can be challenging to ventilate. A similar strategy is used as in COPD. That is, increasing the expiratory time by reducing the respiratory rate and increasing the inspiratory to expiratory ratio. A low minute volume and high PaCO₂ is the result. If there is no surgical requirement for muscle relaxation, pressure support ventilation or spontaneous breathing may allow optimisation of ventilation to perfusion matching, as this allows continued contraction of the diaphragm and other respiratory muscles. (Warner, 2006) The use of

recruitment manoeuvres followed by positive end expiratory pressure may minimize atelectasis and improves oxygenation.

Management of acute intraoperative bronchospasm.

There are many differential diagnoses of intraoperative bronchospasm. They include: mechanical obstruction of the endotracheal tube, inadequate depth of anaesthesia, endobronchial intubation, aspiration, pulmonary oedema, pulmonary embolism, pneumothorax, anaphylaxis and acute asthma.

Bronchospasm may manifest as increased peak inspiratory airway pressure, audible wheeze, decreased pulmonary compliance, decreased PaO₂ and decreased oxygen saturation, decreased tidal volume and hypercarbia.

The essential acute management of bronchospasm in an intubated patient is ensuring adequate oxygenation and ventilation. Increase the inspired oxygen concentration to 100% and ventilate by hand. Hand ventilation will provide information about pulmonary compliance. To verify that the problem is truly bronchospasm, auscultate the chest; check the position, placement and patency of the endotracheal tube (pass a suction catheter, exclude endobronchial placement and kinking). Deepen anaesthesia, cease provoking agents, change ventilation, administer a beta-2 agonist (via a spacer or nebulizer in the circuit), and corticosteroids (which have a delayed onset time). Intravenous lignocaine can attenuate reflex bronchoconstriction related to airway manipulation.

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PREOPERATIVE CARDIAC RISK ASSESSMENT.

Heart disease is a leading cause of death worldwide and its incidence is increasing both within the developed and developing world. Increasingly anaesthetists are requested to provide anaesthesia for non-cardiac surgery in patients at risk of cardiovascular complications. In the USA in 1999 approximately 50,000 patients had a perioperative myocardial infarction (MI) of whom about 40% died (1). Interestingly most perioperative MIs are silent. Possible factors that contribute to silent perioperative MI include the use of analgesia, residual anaesthesia and other perioperative painful stimuli (1). Most are often preceded by long periods of ST depression. In 2003 it was estimated that more than one million patients undergoing non-cardiac surgery in the United States suffered an adverse cardiovascular event (2).

Surgery induces sympathetic stimulation and a hypercoagulable state. Patients with major predictors of risk have a five-time greater perioperative risk of myocardial infarction.

Potential strategies to improve outcome include:

- Preoperative identification of high-risk patients that would benefit from preoperative cardiac revascularisation.
- Improved detection of perioperative ischaemia (ECG, echocardiography).
- Prophylactic use of anaesthetic and anti-ischaemic techniques to decrease frequency and severity of myocardial ischaemia (e.g. beta adrenergic blockade, statins, treat dynamic perioperative predictors).

All patients presenting for anaesthesia require preoperative assessment. The prime function of preoperative assessment is preoperative risk evaluation and reduction to optimise the patient's health and minimise morbidity and mortality. (What is the risk of a complication during and after surgery and how can that risk be reduced or eliminated?)

To enable preoperative risk evaluation and reduction, certain principles must apply. It is important that assessment should be accurate, efficient, and timely and not add risks. No cardiovascular test should be performed if the results will not change perioperative management. The predictive value of testing is optimised when it is applied to an intermediate-risk population, as the incidence of false negatives and false positives is inversely proportional to disease prevalence. Testing a low risk population increases costs and may increase morbidity and cause harm by delaying a non-cardiac operation. Conversely, the outcome of a patient with a clear history of active coronary artery disease will not be modified by screening tests.

The positive predictive value of all stress tests is only 20-30%, whereas their negative predictive value is excellent at 95-100%.

Once the risk is quantified the clinician must consider interventions, however patients must not be subjected to unnecessary interventions that would otherwise not be indicated nor should surgery be unnecessarily delayed. If there is no treatment to lessen the cardiac risk, then the wisdom of additional testing is questionable.

This is important in cardiac risk assessment, as the role of coronary revascularisation specifically to reduce perioperative cardiac risk remains unproven and non-invasive stress testing has relatively poor predictive power that hampers usefulness. Coronary revascularisation prior to non-cardiac surgery should be reserved for those patients with an independent need for the procedure, such as unstable angina or stable angina refractory to medical therapy

In general:

- *Stable patients who have previously undergone recent (? < 5 years) cardiac revascularisation or who have no significant disease on coronary angiography or stress testing within 2 years may safely proceed to non-cardiac surgery provided sufficient time has elapsed for recovery from the revascularisation.*
- *Emergency surgery should proceed without delay.*
- *Elective surgery should be indefinitely delayed for patients with unstable coronary disease.*
- *Low risk patients in good health undergoing low or intermediate risk surgery can proceed without delay or further investigation.*
- *Beta blockade may provide beneficial risk reduction.*

Over the last 25 years many models for assessing preoperative cardiac risk have been described. Goldman et al (1977) were the first to develop a preoperative cardiac risk index for patients undergoing general anaesthesia (4). The nine risk factors identified by Goldman are age, myocardial infarction, congestive cardiac failure (third heart sound or jugular venous distention), aortic stenosis, arrhythmia, general medical condition and nature of surgery.

In 1986 Detsky et al modified Goldman's original multifactorial index (5), adding unstable angina and pulmonary oedema, that enhanced the predictive power. The Detsky score divided patients into three classes; class 1 being low risk and class 111 being high risk.

Eagle (1989) (7) and colleagues identified five clinical predictors of perioperative cardiac events: Q wave on ECG, angina, ventricular ectopy requiring treatment, diabetes with treatment and age > 70 years old. Patients without clinical risk factors had a 3% incidence of perioperative ischaemic events. Patients with two had a 16% incidence and patients with three or more clinical risk factors had a 50% incidence.

After studying 517 patients, Vanzetto (1996) (8) and colleagues added a history of MI, ST segment abnormalities on ECG, hypertension with left ventricular hypertrophy and a history of congestive heart failure to Eagle's predictors.

In 1999, after studying 4,315 patients over 50 years of age undergoing elective major non-cardiac surgery, Lee et al (7) revised Goldman's criteria for cardiac risk index and developed six independent predictors: high risk surgery, ischaemic heart disease, congestive heart failure,

History of cerebrovascular disease, preoperative treatment with insulin and preoperative serum creatinine greater than 2.0mg/dl. Patients are stratified by these variables.

Lee Cardiac Risk Index.

Number of variables.	Risk of major postoperative cardiac complication.
0	0.4%
1	0.9%
2	7.0%
3 or more	11.0%

ACP Guidelines

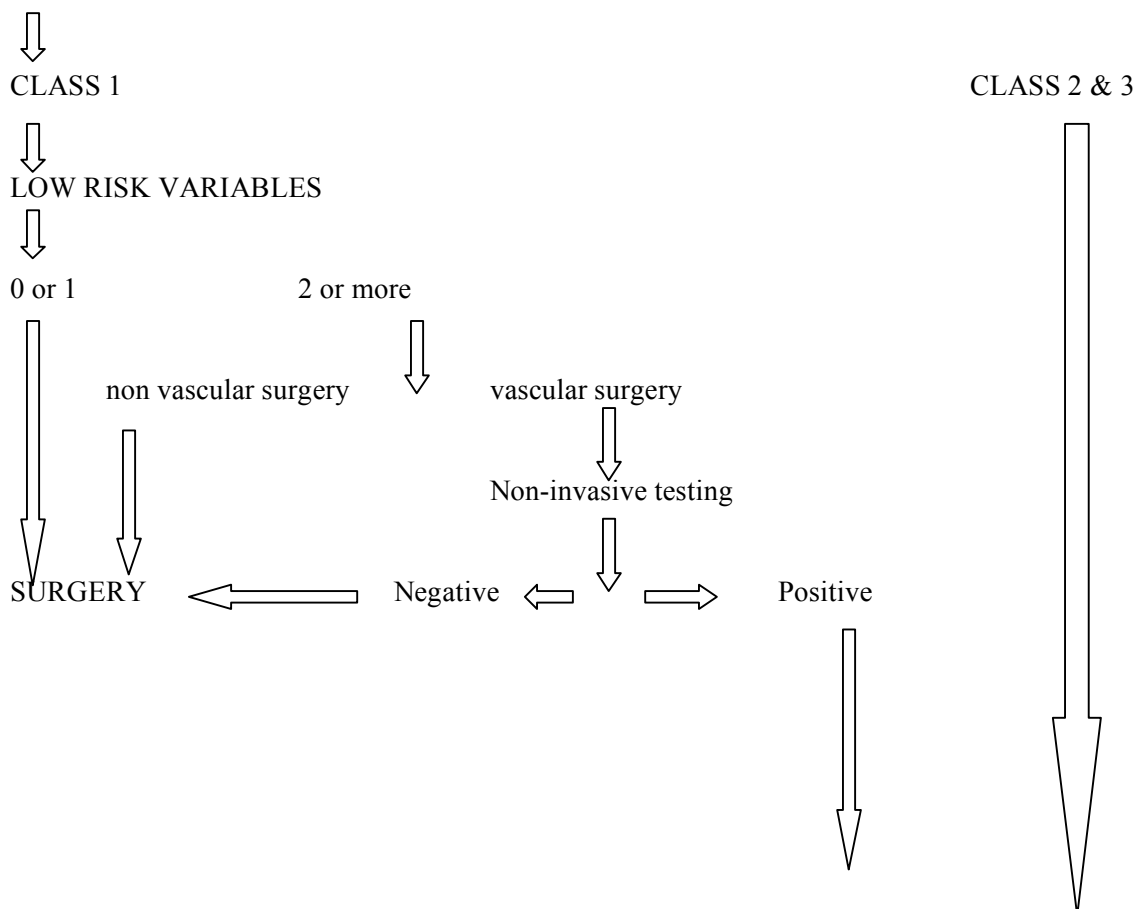
All patients are first evaluated using the Detsky modified cardiac risk index to stratify them into class 1 (low risk) or class 11(intermediate risk) and class 111(high risk).

Class 1 patients are then further stratified using low-risk variables of Eagle and Vanzetto. Class 1 patients with 0 or 1 low risk variables and class 1 patients with 2 or more factors requiring non-vascular surgery proceed to surgery whilst class 1 patients with 2 or more low risk variables requiring vascular surgery have stress testing. Patients with a negative stress proceed to surgery while those with a positive stress test need heart failure and arrhythmias optimised by medical treatment and ischaemic heart disease considered for treatment with revascularisation (independent of the non-cardiac surgery).

Class 11 and 111 patients all require optimisation of heart disease and arrhythmias and or determination of eligibility for coronary revascularisation.

The ACP did not consider the functional status of the patient to be a useful predictor (unlike the ACC/AHA). The ACP guidelines also differ from ACC/AHA in that lower risk patients undergoing vascular surgery require stress testing. (The incidence of perioperative myocardial infarction can reach 34% in vascular surgical patients).

DESTKY MODIFIED CARDIAC RISK STRATIFICATION



Ischaemic heart disease: determine eligibility for coronary revascularisation (decision independent of non-cardiac surgery).

CHF, arrhythmias, valvular disease: optimise medical management and reassess cardiac risk.

Non modifiable factors: cancel or modify surgery

ACC/AHA 2002 Guidelines

In 1996 the American College of Cardiology (ACC) and the American Heart Association (AHA) produced a guideline for preoperative cardiovascular evaluation of non-cardiac patients. The ACC/AHA guideline was updated in 2002 (9). Their guideline/algorithms are based on:

- the patient's clinical predictors,
- the patient's functional status,
- the urgency of surgery.

Emergency procedures proceed directly to surgery.

Patients who have had revascularisation within 5 years and are asymptomatic can also proceed to surgery. Those that are symptomatic and have favourable coronary angiography within 2 years and patients have not had revascularisation within 5 years but have a favourable angiography within 2 years may also proceed with surgery.

All other patients require evaluation of clinical predictors.

Unlike the ACP guidelines the ACC/AHA guidelines include the patient's functional status. This is supported by the study by Reilly DF et al (10). They found an increase in minor complications in a poor exercise tolerance group.

Functional capacity can be evaluated by the estimated energy requirements for various activities, and graded in metabolic equivalents (METS). 1 MET is the oxygen consumption at rest of an adult (3.5 ml/kg/min). 1 -4 METS is equivalent to vacuuming, bathing, dressing, walking around the house or walking 2 blocks at 3-5 km/hr. 5-9 METS is equivalent to climbing 1 flight of stairs, playing golf, dancing or walking on the level at 6 km/hr.

Patients are first assessed for major, intermediate and minor clinical predictors.

Major clinical predictors are unstable angina, recent myocardial infarction (within 30 days), decompensated congestive cardiac failure, significant arrhythmias and severe valvular disease.

[In the 1980s guidelines recommended waiting 6 months after a myocardial infarction before proceeding with non-cardiac surgery. (Two studies (11, 12) from 1972 and 1977 respectively evaluated the incidence of myocardial infarction after general anaesthesia in patients with previous myocardial infarction. Patients who had surgery within three months of infarction had a re-infarction rate of 27 to 37 percent. After three to six months the reinfarction rate was 11 to 16 percent and beyond 6 months the reinfarction rate remained stable at 5 percent). Since then it has become apparent that any event in the coronary circulation (new ischaemia, infarction or revascularisation) induces a high-risk period of 6 weeks and an intermediate-risk period of 3 months. The risk is also related to the functional status of the ventricles and the amount of myocardium at risk of further ischaemia.]

Patients with major clinical predictors need their surgery cancelled or delayed for medical optimisation and re-evaluation of cardiac status. If surgery is deemed necessary they should be considered for coronary angiography.

Intermediate clinical predictors are mild angina (class 1-2), prior MI (history or ECG), treated congestive heart failure, diabetes and renal insufficiency. Most of these are proof of well established but controlled coronary artery disease. Diabetes is included as it is often associated with silent ischaemia and is an independent risk factor for perioperative mortality. These patients need assessment of their functional capacity.

Patients with intermediate clinical predictors and moderate or good functional capacity (>4 METS) or low or intermediate risk procedures can proceed to surgery.

Patients with intermediate clinical predictors and poor functional capacity (<4 METS) or high-risk procedures require non-invasive testing. Those with a positive stress test may require coronary angiography and subsequent revascularisation.

Minor clinical predictors are advanced age, abnormal ECG, arrhythmias, stroke, uncontrolled hypertension. These are markers of an increased probability of coronary artery disease.

Patients with a functional status of less than 4 METS and high-risk procedures require non-invasive stress testing.

Risk reduction strategies.

Perioperative cardiac ischaemic events are principally due to a mismatch of myocardial oxygen supply/demand or coronary artery plaque rupture.

Myocardial oxygen supply/demand must be sustained by maintaining normothermia, treating anaemia, adequate analgesia and tight haemodynamic monitoring (CM5) and control.

Triggers for plaque rupture must be avoided and prophylaxis provided for post-operative hypercoagulability.

Experimentally, halogenated volatile anaesthetics have a protective effect on the ischaemic myocardium, providing pharmacological preconditioning with improved post-ischaemic recovery and smaller infarct size. This seems to be mediated via an effect on the mitochondrial adenosine triphosphate regulated potassium channels triggered by protein kinase C-coupled signalling pathways.

Epidural anaesthesia and analgesia, claim better suppression of surgical stress, more stable haemodynamics, reduced blood loss, improved pain control and peripheral vascular circulation. It seems that primarily patients at higher risk may benefit from general anaesthesia plus an epidural due to improved analgesia and reduced respiratory failure.

The ACC/AHA practice guidelines of 2002 recommended “when possible, beta blockers should be started days or weeks before elective surgery, with a dose titrated to achieve a resting heart rate between 50 and 60 beats/min” but post-operative beta-blocker withdrawal may induce ischaemia and/or arrhythmias. If patients are unable to take oral beta-blockers then preoperative beta blockade may be counterproductive. Current evidence suggests beta blockade reduces perioperative cardiac events in high-risk patients but low or moderate risk patients need further large trials.

Preoperative treatment with statins and good glycaemic control also contribute to reduced perioperative death.

GOLDMAN & DETSKY MODIFIED CARDIAC RISK INDEX		
RISK FACTOR	DETSKY	GOLDMAN
Age greater than 70	5	5
Myocardial infarction within six months	10	10
Myocardial infarction after six months	5	
Canadian Cardiovascular Society angina classification		
Class 111 (angina with walking one to two blocks or climbing one flight of stairs or less at normal pace.	10	
Class 1V (angina with any physical activity)	20	
Unstable angina within six months	10	
Alveolar pulmonary oedema within one week	10	11
Alveolar pulmonary oedema ever	5	
Suspected critical aortic stenosis	20	3
Arrhythmia other than sinus or sinus plus premature beats	5	7
More than 5 premature ventricular beats/minute	5	7
Emergency operation	10	4
Intraperitoneal		3
Major vascular		3
Poor general medical status (pO ₂ < 60mmHg, pCO ₂ > 50mmHg, K < 3mmol/l, HCO ₃ < 20mmol/l, urea >18 mmol/l, creatinine > 260umol/l, chronic liver disease, bed ridden).	5	3

GOLDMAN

Greater than 25	56% death complication	22% severe	cardiovascular
Less than 26 and greater than 5	4% death complication	17% severe	cardiovascular
Less than 6	0.2% death complication	0.7% severe	cardiovascular

DETSKY

Class.	Points.	Cardiac risk.
1	0 to 15	Low
11	20 to 30	
111	31 plus	High

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HYPERTENSION.

The World Health Report of 2002 estimated that hypertension affected 1 billion people around the world and was responsible for 7.1 million deaths per year. The incidence of hypertension is increasing but its control remains inadequate. "More than a quarter of the world adult population is already hypertensive and this number is projected to increase to 29%, 1.56 billion, by 2025" (1). Almost three quarters of the worldwide hypertensive population will be in developing countries.

Hypertension is the most common risk factor for cardiovascular morbidity and mortality. The risk of cardiovascular disease increases progressively as blood pressure increases. The relationship between blood pressure and cardiovascular mortality is positive, strong, continuous and predictive for those with or without coronary heart disease, and it increases with age. Beginning at 115/75 mmHg, an increase of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) in middle-aged and elderly persons is associated with a 2-fold increase in cardiovascular mortality. In individuals older than 50 years, SBP is a more important cardiovascular risk factor than DBP.

[In urbanised populations the systolic blood pressure increases with age as the aorta stiffens. In a healthy aorta the stroke volume ejected during ventricular systole results in some forward blood flow but most ejected blood is stored in elastic arteries. During ventricular diastole, the elastic recoil of the arterial wall maintains forward blood flow for the rest of the cardiac cycle. With increasing age the aorta stiffens and there is decrease diastolic elastic recoil, resulting in a higher systolic pressure and a fall in diastolic pressure. In this way, the prevalence of systolic hypertension increases with age, and for those older than 50, isolated systolic hypertension is the most common form of hypertension.]

Hypertension increases the risk of heart failure at all ages. It precedes the development in 90% of patients and increases the risk of heart failure by 2-fold in men and 3-fold in women. Hypertension is the most important risk factor for stroke and intracranial haemorrhage. It is also a risk factor for chronic renal failure and is associated with an increased incidence of ventricular arrhythmias, death following myocardial infarction and sudden cardiac death. Hypertensive patients are at risk of coronary events and may have a worse prognosis after myocardial infarction. Hypertension is common and carries a worse prognosis in diabetic patients.

Pathogenesis.

The pathogenesis of essential hypertension is poorly understood. A variety of factors have been implicated including increase sympathetic neural activity with enhanced beta-adrenergic responsiveness, increased angiotensin II activity and increased endothelin production with decreased vasodilatation.

Though presumably multigenic, primary hypertension is influenced by environmental factors. Obesity, physical inactivity, excessive sodium intake and excessive alcohol intake all increase the occurrence of persistent hypertension. Persons who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.

Comprehensive lifestyle changes can reduce blood pressure.

There are numerous causes of secondary hypertension including primary renal disease, pheochromocytoma, primary hyperaldosteronism, renovascular disease, Cushing's syndrome, sleep apnoea syndrome, coarctation of aorta and drug induced.

Definition.

Normal (optimal) blood pressure is defined as SBP less than 120 mmHg and DBP less than 80 mmHg.

Prehypertension is defined as a SBP 120 to 139 mmHg or DBP of 80 to 89 mmHg. Prehypertension was first introduced by the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) in 2003. The risks associated with prehypertension are in part related to the tendency of blood pressure to increase with age, thus prehypertension is a precursor of clinical hypertension and consequently of the cardiovascular disease and renal risks associated with elevated blood pressure. The treatment of prehypertension is largely education and lifestyle changes. In patients with diabetes or chronic renal disease, pharmacological treatment must also be considered.

Hypertension is defined as a SBP greater than or equal to 140 mmHg or a DSP greater than or equal to 90 mmHg.

Malignant hypertension is severe hypertension with retinal haemorrhages, exudates or papilloedema.

Drug therapy.

Drug therapy may be expensive and associated with side effects however there is clear evidence that antihypertensive drug treatment is beneficial for hypertension.

- Thiazide diuretics
- Beta-blockers
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin 11 receptor blockers (ARBs)
- Calcium channel blockers

Each of the antihypertensive agents is roughly equally effective, producing a good antihypertensive response in 30 – 50% of cases. There is, however, wide interpatient variability with patients responding to one drug and not others and each class of antihypertensive has advantages and disadvantages that vary with underlying diseases that may be present.

There were three significant conclusions of two meta-analyses of multiple randomised trials from 2003 (2) & (3).

1. Blood-pressure reduction by any drug compared with placebo reduced cardiovascular morbidity and mortality.
2. All classes of drugs reduced total and cardiovascular mortality equally with equal degrees of blood-pressure reduction.
3. Different classes provided differing degrees of protection against individual cardiovascular morbidities.

For example: patients at risk of diabetes should avoid beta-blocker-diuretic treatment combinations. ACE-inhibitors and angiotensin receptor blockers offer improved renal protection. Calcium-channel blockers are marginally better at preventing stroke and the ACE inhibitors perindopril and ramipril gave protection from future myocardial infarction.

However these conclusions are based on limited data and some authors believe that there is sufficient data to make recommendations according to individual cardiovascular morbidity risks. The most compelling advice would be to reduce blood pressure to appropriate levels with whatever drug is available while avoiding adverse effects. Often two or more antihypertensive medications will be required to achieve ideal blood pressure control.

The ALLHAT study strongly suggests a primary role for a **thiazide diuretic** in most patients however thiazides have several adverse metabolic effects including hypokalaemia, hyperuricaemia, mild hypercholesterolaemia and hyperglycaemia. These adverse metabolic effects can generally be avoided by the use of low doses (12.5 to 25 mg hydrochlorothiazide per day). Diuretics are specifically indicated in patients with heart failure. Hypokalaemia can potentially potentiate the effects of muscle relaxants and predispose to cardiac arrhythmias.

Beta-blockers also have adverse metabolic effects including a moderate elevation of plasma glucose, reduced HDL-cholesterol and elevated triglycerides. They may be relatively or absolutely contraindicated with asthma, chronic obstructive pulmonary disease, severe peripheral vascular disease, bradycardia and second or third degree heart block. Beta-blockers may be preferred in patients with tachycardia, congestive heart failure due to diastolic dysfunction and some cases of systolic dysfunction, previous myocardial infarction and angina.

ACE inhibitors can cause a dry hacking cough and angioneurotic oedema. Other side effects include hyperkalaemia, acute renal failure and they are contraindicated during pregnancy. ACE inhibitors are generally effective and lack the adverse lipid and glycaemic effects of thiazides and beta-blockers. The response to thiazide diuretics may be limited by the hypovolaemia induced renin release. ACE inhibitors work synergistically with thiazides preventing the renin release. ACE inhibitors are also relatively indicated for patients with heart failure, myocardial infarction, diabetes, chronic renal failure and left ventricular failure.

ARBs are equally effective as ACE inhibitors and have the same indications for use. ACE inhibitors and ARBs can theoretically blunt the compensatory activation of the renin-angiotensin system during surgery and result in prolonged hypotension. It may be reasonable to consider withholding these medications on the morning of surgery in patients who are taking them for congestive heart failure who also have a low baseline blood pressure.

All three types of **calcium channel blocker** (dihydropyridines, verapamil and diltiazem) are equally effective antihypertensive agents. The calcium channel blockers verapamil and diltiazem should not be used in second and third degree heart block and congestive heart failure with moderate to marked systolic dysfunction.

Some recent trials have questioned the place of beta-blockers and diuretics as the mainstay and often the first choice of drug. Atenolol seemed to provide no cardio-protection and diuretic based regimens with or without beta-blocker provoked more new cases of diabetes. The ASCOT (4) trial was stopped prematurely because of the mortality advantage in the calcium channel blocker-ACE inhibitor group compared to the beta-blocker-diuretic group. More modern beta-blockers such as carvedilol and nebivolol could be safer than older beta-blockers, with less glucose intolerance but this requires further study.

Studies of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in high risk patients have led some experts to conclude that these agents should be recommended in this patient population.

Further studies may confirm these suggestions but the available data is more consistent with the conclusion that the achieved blood pressure, rather than the specific class of drug, is the principal determinant of benefit.

Continuation of antihypertensive medication through the perioperative period is accepted anaesthetic practice and produces greater perioperative haemodynamic stability but the perioperative management of hypertensive patients is more complex. Abruptly stopping some antihypertensive medication may be associated with significant rebound hypertension.

Anaesthesia.

Hypertension is regarded as an added risk factor in anaesthesia. Induction of anaesthesia can cause the blood pressure to rise by 20 to 30 mmHg and heart rate by 15 to 20 beats per minute in the normotensive patient. These responses may be markedly exaggerated with untreated hypertension. Similarly the gradual increase in blood pressure and heart during recovery may be exaggerated in hypertensive patients. Patients with pre-existing hypertension are more likely to experience blood pressure and heart rate lability during anaesthesia.

There are still many controversies about perioperative management of hypertensive patients. In the review paper by Howell et al (6) they suggest that the perioperative management of hypertensive patients can be considered by four different questions.

1. Is having a diagnosis of hypertension of itself associated with increased perioperative risk, regardless of the arterial pressure at the time of admission to hospital for surgery?
2. Is elevated arterial pressure at the time of admission for surgery associated with increased perioperative cardiac risk?
3. What is the importance, if any, of poorly controlled hypertension in the perioperative setting? Is there any interaction between elevated admission arterial pressure and being diagnosed with hypertensive disease previously such that this increases perioperative risk?

4. Does the treatment of elevated admission arterial pressure before surgery reduce perioperative cardiac risk?

In 1929, Sprague (7) identified an association between hypertension and cardiac risk. He reported the death of one-third (12 due to cardiovascular complications) of 75 hypertensive patients in the perioperative period.

In 1971 Prys-Roberts (8) and colleagues recommended that, where possible, hypertensive patients should have anaesthesia and surgery deferred to allow the hypertension to be treated however despite the unequivocal association between hypertension and cardiovascular events, the systematic review and meta-analysis of 30 observational studies by Howell, Sear and Foex 2004, (6) concluded, “studies demonstrated an odds ratio for the association between hypertensive disease and perioperative cardiac outcomes of 1.35 (1.17-1.56). This association is statistically but not clinically significant. There is little evidence for an association between admission arterial pressures of less than 180 mmHg systolic or 110 mmHg diastolic and perioperative complications.” [This and other studies agree with the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines of 2002 which states that mild to moderate hypertension (SBP less than 180 mmHg and DBP less than 110 mmHg) is not an independent risk factor for perioperative cardiovascular complications.] Howell’s conclusion continues: “the position is less clear in patients with admission pressures above this level. Such patients are more prone to perioperative ischaemia, arrhythmias, and cardiovascular lability, but there is no clear evidence that deferring anaesthesia and surgery in such patients reduces perioperative risk”. The ACA/AHA guidelines recommend that elective surgery should be postponed in severely hypertensive patients but currently there is little evidence available to support this statement. Though it appears that severe perioperative hypertension by itself may have limited significance the anaesthetist must be aware of end organ damage. It is clear that the higher the hypertension, the greater the risk of end organ damage and perioperative risk.

Longnecker described swings in arterial pressure over a wide range in hypertensive patients as “Alpine Anesthesia”. There is limited direct data to support achieving haemodynamic stability however it is a common belief that this is more important than the absolute value of intraoperative blood pressure control. The anaesthetist should aim to at least prevent arterial pressure fluctuations of greater than 20% of baseline.

The most important risk factor for postoperative hypertension is a history of preoperative hypertension. Patients with postoperative hypertension should be investigated for treatable causes e.g. pain, anxiety, hypercarbia, hypoxia, hypervolaemia, drug withdrawal, drug side effects and bladder distention. The patient’s usual oral antihypertensive medication or a comparable parenteral alternative should be given immediately postoperatively.

A direct association between preoperative hypertension and perioperative complications is unclear. There appears to be general agreement that patients with only mild to moderate

hypertension should not have their surgery delayed to allow time to control their hypertension. Though evidence is lacking most guidelines still recommend that it would be prudent to delay surgery for patients with severe hypertension. The options available to the anaesthetist are to ignore the elevated arterial pressure and proceed, initiate acute treatment to control arterial pressure before proceeding with surgery or delay surgery for a period of several weeks to allow control of blood pressure. These recommendations apply to hypertension alone. Hypertension is a main determinant of end organ damage and surgery may need to be delayed in order to quantify/treat end organ dysfunction. The greater the degree of hypertension the greater the risk of end organ damage. As with all patients the urgency and benefit of surgery must be balanced against the risk of delay.

When confronted with a hypertensive patient preoperatively the anaesthetist should:

1. Assess the urgency and benefit of surgery.
2. Assess the patient's overall cardiovascular risk status.
3. Identify treatable causes of hypertension.
4. Determine the extent of end organ damage. (Delaying surgery in hypertensive patients will be justified if the delay allows time to quantify the degree of dysfunction and/or improve the end organ function. The greater the hypertension the greater the chance of end organ damage.)
5. Ensure strict cardiovascular management to ensure perioperative/intraoperative haemodynamic stability.
6. Continue antihypertensive medication throughout the perioperative period.

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ADDENDUM

Drugs for the management of hypertensive emergencies.

DRUG	CLASS	DOSAGE
CLONIDINE	Alpha 2 blocker	25-150µg 8 hrly
ESMOLOL	Beta blocker	0.5mg/kg
GTN	Venodilator	5-100µg/min
HYDRALAZINE	Vasodilator	10-20mg 3-4 hrly
MAGNESIUM	Vasodilator	4gm bolus + 1gm/hr
METOPROLOL	Beta blocker	1mg prn, 1-5mg/hr
NITROPRUSSIDE	Vasodilator	Commence at 10µg/kg/min
PHENTOLAMINE	Alpha 2 blocker	1mg prn, 5-30mg/hr

For some conditions there are antihypertensives preferably avoided:

- Cerebral vasodilators (eg nitroprusside and hydralazine) in the presence of hypertensive encephalopathy.
- Beta-blockers alone for phaeochromocytoma.
- ACE inhibitors and diuretics in the presence of renal dysfunction.
- Any anti-hypertensive for intracranial hypertension or intracranial haemorrhage.

HYPERTENSIVE EMERGENCIES.

Introduction.

A hypertensive emergency is severe hypertension associated with acute end-organ damage (acute pulmonary oedema, subarachnoid or intracranial haemorrhage, aortic dissection and malignant hypertension with or without hypertensive encephalopathy) and should be immediately but carefully reduced (usually intravenous). Excessive acute reduction of severe hypertension can cause ischaemic complications including stroke and myocardial infarction. Therefore patients with severe hypertension, but who are asymptomatic (hypertensive urgency) should have a slower reduction (oral medication).

Hypertensive crisis is defined as a critical elevation in blood pressure in which diastolic pressure exceeds 120 mmHg.

[Malignant hypertension is marked hypertension with retinal haemorrhages, exudates or papilloedema. It is usually associated with a diastolic pressure greater than 120 mmHg. Hypertensive encephalopathy can occur in previously normotensive patients with an acute rise in blood pressure to as low as a diastolic pressure of 100 mmHg. Hypertensive encephalopathy is characterised by the insidious onset of headache, confusion concluding with seizures and coma and reflects cerebral hyperperfusion, loss of autoregulation, and disruption of the blood brain barrier. Severe hypertension is usually defined as a diastolic pressure greater than 120 mmHg].

Causes.

Hypertensive crisis occurs most often in patients with a history of pre-existing hypertension and inadequate treatment or non-adherence to management or abrupt withdrawal of antihypertensive agents.

Secondary causes include: renovascular hypertension, chronic renal disease, acute glomerulonephritis, post-renal transplantation, drugs (cocaine, LSD, PCP), ingestion of tyramine-containing food, or other sympathomimetics combined with MAO inhibitor therapy, preeclampsia, pheochromocytoma, Cushing's syndrome head injury, aortic dissection, aortic coarctation, renin or aldosterone secreting tumour, vasculitis and autonomic hyperactivity in the presence of spinal cord syndromes.

Evaluation.

Evaluation should aim to distinguish between hypertension urgency and hypertension emergency and thus determine the mode of treatment, symptoms related to severe elevations in blood pressure and end organ damage.

The history should enquire about previously diagnosed hypertension and compliance with treatment and seek possible secondary causes. Examination should include standing and supine

blood pressure measurement, fundoscopy, cardiovascular examination for heart failure or aortic dissection and neurological examination for neurological compromise.

Investigations should include FBE, urinalysis (haematuria, casts) Urea & electrolytes (elevated urea and creatinine and metabolic acidosis of renal failure, hypokalaemia secondary to hyperaldosteronism), ECG and echocardiography (LVH and myocardial ischaemia), CXR (pulmonary oedema, widen mediastinum).

Treatment options.

Several parenteral and oral antihypertensive drugs are available for the management of hypertensive emergencies. The goal is for a prompt (several minutes to several hours) but controlled reduction of blood pressure usually aiming for a 20-25% reduction in mean arterial pressure (eg. 10% reduction in the first hour and another 15% reduction over the next 2 to 3 hours). The pressure should be reduced sufficiently to relieve symptoms but not to a point that causes end-organ ischaemia. The exception to this management is aortic dissection, for which the target may be a systolic blood pressure of less than 120 mmHg within 20 minutes.

Nitroprusside is both a dilator of arterioles and veins. It is very effective, predictable and as its onset is within seconds and offset within minutes, nitroprusside can be accurately titrated to effect. However because of its rapid and extremely potent effect, nitroprusside requires constant (preferably intra-arterial) blood pressure monitoring.

Nitroprusside combines with haemoglobin to produce cyanmethaemoglobin and cyanide ions that are enzymatically converted to thiocyanate that is excreted in the urine. Therefore nitroprusside can potentially cause cyanide or thiocyanate toxicity (lactic acidosis and altered mental status). To minimise this risk, prolonged infusions (>24 to 48 hours) and high infusion rates must be avoided. (Never administer the maximum dose of 10 micrograms/kg/min for more than ten minutes). As thiocyanate is removed almost exclusively by the kidneys with a half-life of approximately 1 week, rates should also be adjusted with renal insufficiency. The toxicity of nitroprusside makes it less than an ideal agent.

Nitroprusside should be used with extreme care in patients with compensatory hypertension, uncorrected anaemia or hypovolaemia, inadequate cerebral circulation and impaired renal function.

Usually the 50 mg vial is added to 100 ml of 5% glucose only giving a 500 microgram/ml solution (10 microgram/min = 1.2 mL/hr). The recommended starting dose is 0.25 to 0.5 micrograms/kg/min adjusted to achieve the desired blood pressure.

Glyceryl Trinitrate (GTN) relaxes vascular smooth muscle producing both arterial and venous dilatation. Venous effects predominate, resulting in decreased venous return to the heart, and reduced preload. Arteriolar relaxation reduces systemic vascular resistance and after load. The net effect is usually a decreased myocardial oxygen demand and reduced systolic, mean and diastolic pressure. Most studies show a slight fall or no change in cardiac output. Like nitroprusside, GTN has a similar fast and short duration of action and is extremely potent, requiring close haemodynamic monitoring and careful titration.

The initial dose of GTN is 5 micrograms/min. 30 mg may be added to 500 ml of 5% dextrose giving a final concentration of 60 microgram/ml (5 microgram/min = 5 ml/hr). Increase the infusion rate in increments of 5 micrograms/minute every 3 to 5 minutes with an upper infusion rate of 50 micrograms/minute.

Hydralazine is a direct arteriolar vasodilator with less predictable and less titratable effect than GTN. The hypotensive effect occurs within 10 to 30 minutes and last 2 to 4 hours. The initial dose is usually 5 to 10 mg with a maximum dose of 20 mg. Hydralazine is often favoured in pre-eclampsia along with magnesium.

Clonidine is a centrally acting alpha 2-receptor antagonist that reduces sympathetic tone. This results in arteriolar and venous dilation with little effect on heart rate or cardiac output. As with GTN and nitroprusside the blood pressure should be intensively monitored during administration. Clonidine is contraindicated in sick sinus syndrome and heart block. Clonidine has central nervous system effects and may potentiate the affect of other centrally acting drugs such as sedatives and hypnotics and should be avoided in hypertensive encephalopathy. Patients with hepatic or renal impairment may require lower dosage.

Clonidine is a very useful agent for controlled acute management of a hypertensive crisis. For a hypertensive crisis the suggested dosage is 150 to 300 micrograms given slowly over 5 minutes. This dose can be repeated every 3 to 6 hours up to 750 micrograms daily.

Phentolamine is an alpha-adrenergic blocker. Its use is limited to the treatment of hypertensive states due to increased catecholamine activity eg phaeochromocytoma.

Nicardipine is dihydropyridines calcium antagonist that has been used to control perioperative hypertension in cardiac surgery patients. Nicardipine also reduces cerebral ischaemia. It has intermediate onset and duration of action Side effects include reflex tachycardia, headache, nausea & vomiting. It should not be used in patients with hear block, acute myocardial infarction, and renal failure.

Fenoldopam is a selective agonist of dopaminergic 1 receptors which produces vasodilatation with rapid onset.

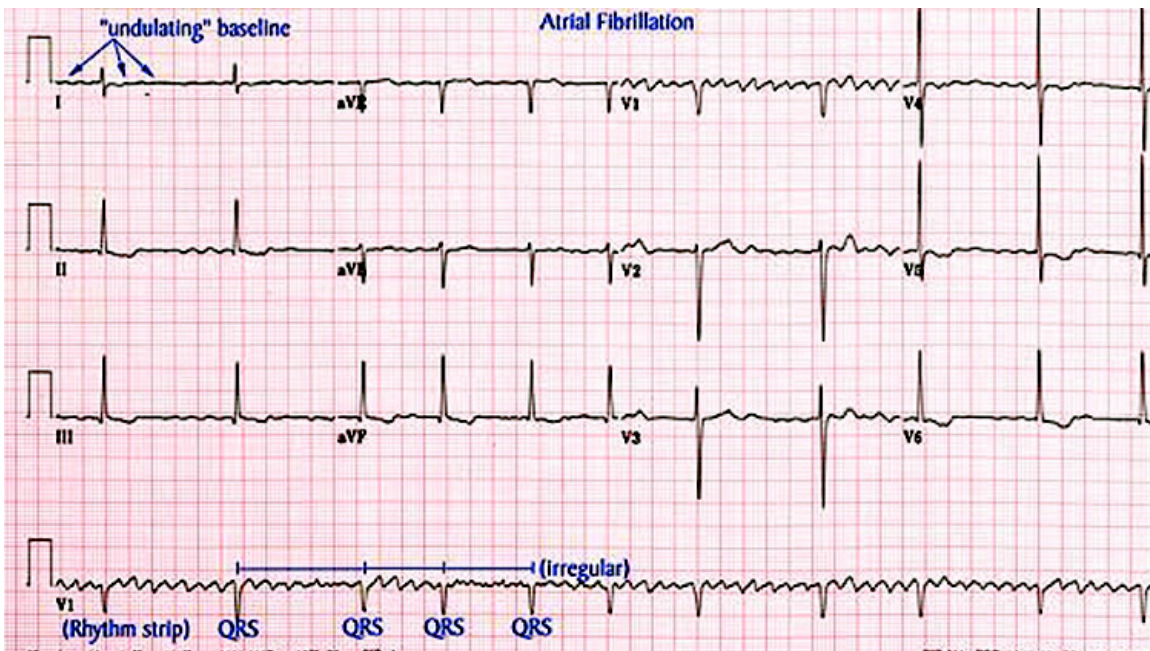
ATRIAL FIBRILLATION.

Atrial fibrillation (AF) is the most common cardiac arrhythmia (3-4% in patients over the age of 60). It is often associated with structural heart disease or systemic disease, being both an indicator of active physiological stressors on the body and an indicator of future cardiac disease progression, but can also occur with no detectable disease (lone AF). Diabetes, hypertension and ventricular hypertrophy are commonly associated with non-valvular AF. It's incidence increases with age and is 1.5 times more common in men.

The thrombo-embolic events and cardiac dysfunction of atrial fibrillation is responsible for considerable morbidity and mortality.

Definition.

AF is a supraventricular arrhythmia characterised by complete absence of co-ordinated atrial contractions. P waves are absent, being replaced by fibrillatory waves (best seen in V1, I, II & aVF).



The complete absence of co-ordinated atrial contractions (350-900/minute) is associated with an irregular and frequently rapid ventricular response rate (90 to 170/minute or often higher). Usually A-V conduction is intact and therefore R-R intervals are irregular.

(In certain circumstances, regular R-R intervals can occur with AF such as A-V block, interference by ventricular or junctional tachycardia, digoxin toxicity and in individuals who are ventricularly paced).

Once the anaesthetist has identified AF they must assess the following, prior to proceeding with anaesthesia

- Patient stability (cardiovascular and co-morbidities),
- AF symptoms (fatigue, palpitations),
- Underlying aetiology and cardiac dysfunction,
- Ventricular rate,
- Risk factors for thrombo-embolic events and bleeding.

Classification.

AF may be classified by its pattern of evolution and response to treatment.

- **First onset** less than 48 hours.

- **Paroxysmal** recurrent episodes, self-limiting, usually minutes to hours, occasionally days.

- **Persistent** not self terminating without drug or electrical cardioversion.

- **Permanent**

An important concept is that as AF continues over time, it is believed that both electrophysiological and structural remodelling of the atria occurs. This remodelling promotes the continued existence of AF. (Thus there is a progression from paroxysmal to persistent to permanent AF).

Pathophysiology.

The pathophysiology of AF is unclear. Classic theories have implicated the presence of multiple circuit re-entry, single circuit re-entry or rapidly discharging atrial focus with fibrillatory conduction. In some circumstances there may be enhanced automaticity within sleeves of atrial tissue that extend into the pulmonary veins or vena caval junctions that generate multiple atrial ectopics (3). With chronic AF the arrhythmia may be maintained by multiple re-entering and randomly circulating wavelets that collide and divide into daughter wavelets (4). Eventually, electrical and structural remodelling of the atria may result in permanent AF (5).

Other influences in the development and maintenance of AF include the autonomic nervous system, atrial stretch, renin-angiotensin-aldosterone system and systemic and local inflammatory diseases.

Causes and risk factors.

In the minority of cases there may be a directly related acute reversible cause including alcohol binge, myocarditis, pericarditis, pulmonary embolism, pneumonia and hyperthyroidism. AF may be precipitated by high vagal tone or high sympathetic tone (ischaemic heart disease, stress, caffeine, sepsis, hypovolaemia, GI bleed).

The majority of patients will have recognised risk factors (especially older age, hypertension, diabetes and ischaemic heart disease). Rheumatic fever valvular disease is a common association in developing countries whilst AF occurs in 27-37% of cardiac artery bypass surgery and 50% of valvular surgery. (Factors related to the development of post-cardiac surgery AF include advanced age, male gender, previous AF, HT, COAD, chronic renal failure, previous cardiac surgery, prolonged p waves, atrial dilatation, high left ventricular pressure, cardiomegaly, right coronary artery grafting, prolonged bypass time and inadequate cardio-protection and hypothermia) (2).

AF is often associated with cardiovascular disease (following myocardial infarction, HT especially if associated with left ventricular hypertrophy, valvular heart disease, congenital heart disease, mainly atrial septal defects and sick sinus syndrome).

A small percentage of the atrial fibrillation population will have a family history and genetic basis.

Management.

The recognition AF mandates investigation into aetiology, risk factors and stroke risk.

The principles of management are (2):

1. Resuscitation
2. Restoration of Sinus Rhythm by pharmacological or electrical means and prevention of recurrence of paroxysmal or persistent AF following restoration of sinus rhythm.
3. Control of Ventricular rate during paroxysmal or persistent AF, and chronically in those with permanent AF.
4. Prevention of thrombo-embolic events.

Rhythm control vs rate control.

Emergency cardioversion.

The first principle of the management of AF is to recognise critically ill patients who require urgent cardioversion. Instability applies both to vital signs and overall clinical status (eg pulmonary oedema, altered mental state and severe chest pain). Immediate electrical cardioversion is indicated in patients with a rapid ventricular rate who are severely haemodynamically unstable or have evidence of acute myocardial infarction or heart failure or in unstable patients who do not respond promptly to drug cardioversion.

Elective cardioversion.

Traditionally it was assumed that the best management was to aggressively treat persistent AF to maintain the patient in SR. However recent trials (AFFIRM, PIAF, RACE, STAF) suggest that rate control of AF may be as effective as restoration of sinus rhythm (measured by symptom control and survival) in stable older patients. The AFFIRM (atrial fibrillation follow-up investigation of rhythm management) assessed 4,060 patients with chronic AF and risk factors for stroke and found no difference in the ischaemic stroke rate between rate and rhythm control groups.

The 2003 guidelines from the American College of Physicians and American Academy of Family Physicians recommend rate control with long-term anticoagulation for most patients with AF.

Patients that may be managed with elective drug cardioversion could include:

- Patients who fail rate control treatment,
- Patients who have contraindications to anti-coagulation and
- Younger patients.

Before attempting cardioversion the anaesthetist must assess the possibility of thrombus in the fibrillating atria, which may dislodge with restoration of sinus rhythm.

Rhythm control.

Rhythm control (cardioversion) - electrical.

Direct current cardioversion has a success rate of 65-99%, however the relapse rate is also high (25-50% at one month).

The traditional progression of charge for monophasic cardioversion is 200J, 200J, 300J and finally 360J (less for biphasic defibrillators).

Brief arrhythmias are common immediately after direct current cardioversion, especially ventricular ectopics, supraventricular ectopics, bradycardia and brief sinus arrest. VT and VF are possible. Patients with hypokalaemia and digoxin toxicity are at higher risk. Patients with underlying conduction defects (these patients usually have a slow ventricular response rate without treatment) may develop profound bradycardia, complete heart block and asystole.

Rhythm control (cardioversion) – drug.

The decision to pharmacologically restore sinus rhythm must be carefully decided. 60% of recent onset AF will spontaneously reverse within 24 hours to a few days and available effective drugs are not without serious side effects. The adverse effects of antiarrhythmic medications may be greater than the benefit of restoring sinus rhythm. There is also a significant chance of recurrence. A strategy to maintain a lower heart rate along with adequate anticoagulation may be a preferable alternative.

Up to 90% of AF can be successfully restored to sinus rhythm if treated within 7 days.

Medications for Cardioversion of Atrial Fibrillation to Sinus Rhythm (1)

Drug	Dosage	Route	Odds ratio of conversion over placebo	Side effects
Ibutilide	1mg over 10 minutes	I.V.	30.7	QT prolongation torsades de pointes
Flecainide	200-300mg oral 1.5-3mg/kg IV over 20 min	Oral/IV	13.2	Hypotension, rapid atrial flutter
Propafenone	450-600mg oral 1.5-2mg/kg IV over 20 min	Oral/IV	3.9	Hypotension, rapid atrial flutter
Amiodarone	1.2-1.8g/day oral divided until 10g total 5-7mg/kg IV over 60min, then 1.2-1.8g/day IV infusion until 10g	Oral/IV	3.2	Hypotension, Bradycardia, QT prolongation. Torsades de pointes, GI complaints
Dofetilide	Renal dosing	Oral	6.7	QT prolongation, torsades de pointes

Amiodarone may be the drug of choice in patients with ventricular dysfunction and ischaemic heart disease. It also has the advantage of prompt rate control.

Maintenance of sinus rhythm may require a class 1 or 11 antiarrhythmic drug. Anticoagulation is recommended in patients with risk factors despite conversion to sinus rhythm.

Rate control.

Controlling the ventricular rate will also increase cardiac output; decreases metabolic demand and avoid adverse effects of antiarrhythmic drugs.

Patients with a suspected underlying cause for the AF (e.g. pulmonary disease) should have rate control. The vast majority will spontaneously revert to sinus rhythm once the underlying cause is treated.

Rate control is generally achieved by drugs that predominantly affect conduction through the AV node.

Several classes of drugs are effective in controlling the ventricular rate and their selection is based on the individual clinical circumstances. For example beta-blockers are a good choice for patients with rapid AF and potential myocardial ischaemia as they provide effective rate control and a mortality benefit in the setting of acute coronary syndrome.

Propranolol may be an appropriate choice in AF associated with thyrotoxicosis as it blocks the peripheral conversion of T3 to T4.

Traditionally digoxin has been preferred in patients with heart failure but there is increasing evidence to support beta-blockers. Digoxin has a significant side effect profile and takes hours to be effective. In stable acute (paroxysmal) AF, calcium channel blockers and beta-blockers are preferred to digoxin because of their rapid onset. Digoxin may be suitable for permanent AF in sedentary patients. Younger active patients will need either a beta-blocker or calcium channel blocker to prevent exercise induced tachycardia.

Patients with Wolf Parkinson White (WPW) and AF may have a very rapid ventricular rate. Unstable patients will need electrical cardioversion. Drugs that act on the AV node (beta-blockers, calcium channel blockers, digoxin and adenosine) are all contra-indicated since may increase conduction by the abnormal pathway. (Patients with sick sinus syndrome and AF usually require pacing).

Amiodarone is useful for patients with a low ejection fraction (<40%) and is good for patients with wide complex tachycardias of uncertain origin as it is effective against both ventricular and supraventricular tachycardias.

Magnesium is a safe, effective, readily available and cheap choice for acute rate control.

Rate control medications for AF with rapid ventricular response (1)

Drug	Loading dose	Maintenance dose	Onset	Side effects	Patient population	Conversion rate	Remarks
Diltiazem	0.25 mg/kg IV over 2 min	5-15mg/hr	2-7min	Hypotension Decreased AV conduction	Stable	50-66%	?prime with calcium to prevent hypotension
Metoprolol	2.5-5mg IV over 2 min up to 3 doses		5min	Hypotension Decreased AV conduction Bronchospasm	IHD Thyrotoxic	57%	Avoid using with calcium channel blocker
Esmolol	0.5mg/kg over 1 min	0.05-0.2mg/kg/min	5min	Hypotension Decreased AV conduction Bronchospasm	IHD Thyrotoxic	80%	
Magnesium	1g over 20min	Variable	5min	Hypotension		60-78%	
Amiodarone	150mg IV over 10min	1mg/min for 6hr then 0.5mg/min for 18hr	20min	Hypotension	Wide complex tachycardia	43-80%	
Digoxin	0.25mg IV up to 1.5mg		2hr	Dig toxicity	Refractory to first-line drugs		Second-line drug

All rate control drugs have the potential to spontaneously convert the patient back to sinus rhythm. Therefore all patients must have risk stratification of thrombo-embolic disease and appropriate preventative treatment.

Non-pharmacological management strategies include atrial pacing, atrial defibrillators and ablation therapy.

Prevention of thrombo-embolism.

The ischaemic stroke risk in AF varies across the range of ages and cardiovascular co-morbidities. Anti-coagulation also has risks (and rarely is contraindicated). Therefore all patients must be individually assessed and their thrombo-embolic risk stratified before commencing anti-coagulation.

AF of less than 48 hours duration has a very low risk of thrombo-embolism and may not require anti-coagulation (but the risk is not zero and the patient may not know when the AF started!). Patients for elective cardioversion should have warfarin for 3 to 4 weeks prior to cardioversion. (INR 2 to 3). Patients for emergency cardioversion should receive heparin. All patients should have warfarin for 3 to 4 weeks after cardioversion unless contraindicated.

Chronic AF is associated with a 3 to 7% annual risk of ischaemic stroke. The incidence of stroke is five times greater and is twice as likely to be fatal in the AF population.

The CHADS2 risk index (6) is one way of identifying patients at risk for ischaemic stroke. The patient is awarded 1 point for a history of congestive heart failure (C), hypertension (H), age > 75(A), diabetes (D) and two points for a history of stroke (S2).

The risk of stroke as a percentage per year is:

CHADS2 score	0	1	2	3	4	5	6
% risk	1.9	2.8	4.0	5.9	8.5	12.5	18.2

A score of 0 is low risk and may be treated with aspirin 325mg/day. A score of 1 or 2 is moderate risk and may receive aspirin or warfarin. A score of 3 or greater is high risk and needs warfarin.

Anaesthesia and AF.

The anaesthetist will frequently be involved with patients who have AF.

- AF is the most common arrhythmia.
- Elective (and often emergency) electrical cardioversion will require sedation/general anaesthesia.

- As AF can be asymptomatic and it may be first detected by the anaesthetist during the preoperative assessment.
- The physiological dysfunctions associated with disease requiring surgery/anaesthesia may precipitate new AF or aggravate existing AF.

The principles of management are outlined above. (Resuscitation/emergency electrical cardioversion, investigation of treatable aetiology and associated co-morbidities, assessment and optimisation of associated co-morbidities, rate (or ?rhythm) control and thrombo-embolic prophylaxis).

In general

- Unstable patients (marked cardiovascular instability or severe symptoms) need electrical cardioversion.
- Elective patients with uncontrolled AF should be deferred for investigation and management.
- Emergency patients require rate control and extensive assessment of treatable aetiologies and associated co-morbidities before surgery if possible. Most emergency surgery can be delayed whilst the patient has rate control, clinical assessment and basic investigations of electrolytes/renal function, full blood count, thyroid function tests, 12 lead ECG and chest x-ray.
- Intraoperative management of rapid AF will need emergency cardioversion or rate control depending on cardiovascular stability then further investigation to determine possible aetiology and assessment of co-morbidity.

Magnesium is an effective treatment for rate control. Beta-blockers may have added benefits in AF with myocardial ischaemia. Amiodarone is useful in low cardiac output states and wide complex tachycardias. Digoxin has a very slow onset.

Most patients on warfarin can have the warfarin omitted for 5 days prior to surgery then recommenced after surgery. High-risk patients will require heparin cover.

VAUGHAN WILLIAMS

CLASS 1	Na CHANNEL BLOCKADE	
Class 1A	Prolong repolarisation	Quinidine, Procainamide, Disopyramide
Class 1B	Shorten repolarisation	Lidnocaine, Mexiletine, Tocainide, Phenytoin
Class 1c	Little effect on repolarisation	Encainide, Flecainide, Propafenone
CLASS 2	Beta-adrenergic blockade	Propranolol, esmolol, L-sotalol
CLASS 3	Prolong repolarisation (K channel blockade and other)	Amiodarone, Bretylium, Ibutilide, d-Sotalol
CLASS 4	Ca channel blockade	Verapamil, Diltiazem
	Miscellaneous	Adenosine, Digitalis, Mg

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ANTICOAGULATION AND NEURAXIAL ANAESTHESIA.

The first reported epidural haematoma after neuraxial anaesthesia under unfractionated heparin was in 1952 (1).

More recently the routine acceptance of protocols for the prevention of thrombo-embolic disease and the introduction of more efficacious anticoagulants and antiplatelet drugs has increased the complexity of managing the anticoagulated patient and neuraxial anaesthesia and analgesia. Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulation administration and patient monitoring. Vigilance in monitoring is critical to allow prompt intervention. Retrospective analysis demonstrates that immediate recognition and intervention within 8 hours is required to prevent neurological deficits or at least limit the deficits (2). Concomitant administration of other drugs affecting haemostasis will increase bleeding risk.

Due to the very low incidence of bleeding complications, guidelines are based solely on retrospective analyses of case reports and pharmacological considerations. Older agents such as heparin and non-steroidal anti-inflammatory drugs have a long history of use and therefore recommendations have a solid basis. Newer agents need a more conservative approach. There is currently not enough information available to make any firm statements with regard to the safety of combining regional anesthesia and new anticoagulants. The newer agents, selective Xa inhibitors, glycoprotein 11b/111a receptor antagonists and direct thrombin inhibitors have superior efficacy with more profound anticoagulant action however reversal agents are mostly not available.

Authors have calculated, by retrospective analysis and case reports, the risk of epidural haematoma after neuraxial techniques without anti-thrombotic drugs to be 1:200,000 to 1:2,000,000. The rarity of spinal haematoma defies a prospective-randomised study.

Neuraxial anaesthesia and thrombolytic therapy.

Patients receiving fibrinolytic or thrombolytic drugs should not receive spinal or epidural anaesthesia/analgesia. There is no data on the safety interval for the performance of neuraxial techniques or catheter removal after thrombolytic drugs. Guidelines recommend avoiding thrombolytic drugs for 10 days after puncture of non-compressible vessels. Patients who have had neuraxial procedures around the time of thrombolytic agents administered must be carefully monitored for neurological deficits. There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. The measurement of fibrinogen level (one of the last clotting factors to recover) may be helpful in making a decision about removal or maintenance.

Neuraxial anaesthesia and low dose unfractionated heparin (UFH).

There is no contraindication to performing neuraxial anaesthesia under low dose UFH, however it may be wise to delay heparin administration until after the performance of the block if technical difficulty is anticipated.

From a pharmacological point of view, the action of heparin peaks at 2 hours after subcutaneous injection, therefore if low dose UFH is initiated before placing a neural block, the procedure may best be delayed for 4 hours. Several days of low dose UFH can induce thrombocytopenia in approximately 1% and may even cause full anticoagulation 2-4%. These patients may require estimation of platelet count prior to any neuraxial procedure.

Neuraxial anaesthesia and intravenous UFH.

Combining neuraxial anaesthesia and intravenous heparin during vascular surgery appears acceptable however it should be avoided in patients with other coagulopathies and guidelines recommend heparin administration should be delayed for 1 hour after needle placement. Current data does not support cancellation if there is a bloody or difficult neuraxial procedure.

Full intravenous heparinisation eg: cardiac surgery, will significantly increase the risk of bleeding complications during regional anaesthesia. Postoperative monitoring of neurological function and selection of a solution that minimises sensory and motor blocked is recommended. Needle placement and catheter removal should only be performed if intravenous administration of heparin has been ceased for 4 hours and coagulation tests are normal. In the case of a bloody tap, conservative guidelines recommend delaying surgery 6 to 12 hours.

Neuraxial anaesthesia and low molecular weight heparin (LMWH) thromboprophylaxis.

Extensive experience with enoxaparin 40mg daily shows that it does not appear to increase the risk of spinal haematoma, if guideline recommendations of an interval of 10-12 hours before needle puncture or catheter removal and delaying the next LMWH dose 4 hours after needle placement are adhered to. The first dose of LMWH should be delayed 24 hours after traumatic needle or catheter placement. Concomitant administration of medications affecting haemostasis represent an additional risk of haemorrhagic complications. Unfortunately the anti-Xa level is not predictive of the risk of bleeding.

Neuraxial anaesthesia and therapeutic low molecular weight heparin (LMWH).

Therapeutic LMWH for acute coronary syndrome, DVT etc (eg enoxaparin 1mg/kg 12 hourly, 1.5 mg/kg daily or dalteparin 120 U/kg 12 hourly) is a contraindication to neuraxial procedures and procedures should be delayed at least 24 hours.

Neuraxial anaesthesia and warfarin.

Neuraxial anaesthesia under warfarin therapy is contraindicated and should not be attempted until the INR is at least 1.5 or lower. Even at an INR of 1.5 there may still be clinically relevant

decreases in factors 11 and X. Therefore a patient's individual situation must always be evaluated and an INR of 1.3 would be a safer limit. Warfarin should be stopped 4 to 5 days prior to the planned procedure.

Neuraxial anaesthesia and non-steroidal antiinflammatory drugs (NSAIDs).

NSAIDs are not seen as a major risk factor for spinal/epidural haematoma.

Neuraxial anaesthesia and thienopyridine and platelet GP 11b/111a inhibitor therapy.

There is no wholly accepted test, including bleeding time, which will guide antiplatelet therapy. Based on pharmacology and surgical reviews, the suggested time interval between discontinuation of ticlopidine and clopidogrel and neuraxial blockade is 14 and 7 days respectively.

The platelet GP 11b/111a inhibitors prevent platelet aggregation. Neuraxial techniques should be avoided until platelet function has recovered (24-48 hours for abciximab and 4-8 hours for eptifibatid and tirofiban).

Neuraxial anaesthesia and herbal therapy.

Herbal drugs, by themselves, appear to represent no added significant risk for the development of spinal haematoma in patients having epidural or spinal anaesthesia.

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PERIOPERATIVE MANAGEMENT OF WARFARIN.

Patients undergoing superficial elective surgery may have their oral anticoagulation continued at a lower therapeutic level (INR 1.5 to 1.8). Patients undergoing deeper or major elective surgery should be stratified as high or low risk of thrombosis if their oral anticoagulation is ceased.

RISK OF THROMBOSIS.

	LOW	HIGH
AF/Cardiomyopathy	No stroke or arterial embolisation in last 12 months	Stroke or systemic embolus in last 12 months
Biological heart valve	> 3 months after implantation	< 3 months after implantation
Prosthesis	Mechanical aortic valve Vascular graft	Mechanical mitral valve
Venous thrombosis	None in last 3 months No hypercoagulable state	Within 3 months Recurrent thrombosis
Systemic arterial embolism	Non-recurrent	Recurrent
NOTE: two low risk factors = high risk.		

PERIOPERATIVE MANAGEMENT.

DAY	LOW RISK	HIGH RISK
-5	<i>Cease warfarin</i>	<i>Cease warfarin</i> <i>Check INR</i> <i>Start full anticoagulation with LMWH</i>
-4		
-1		<i>Stop LMWH at least 18 hrs preoperatively.</i>
DAY OF SURGERY	<i>Check INR, if >2 consider postponement, FFP</i>	
+1	<i>Recommence warfarin at usual dose.</i>	<i>Recommence LMWH</i> <i>Start warfarin at usual dose</i> <i>Cease heparin when INR >2</i>

VALVULAR HEART DISEASE – GENERAL PRINCIPALS.

Background.

Valvular heart disease is found in up to 4% of patients >65 years of age. (1) Murmurs, reflecting underlying valvular disease, may be discovered incidentally during preoperative assessment.

Regardless of the valvular lesion or its underlying cause, the preoperative assessment of the patient should be primarily concerned with determining:

- The significance and severity of the lesion (based on the proposed surgery).
- The haemodynamic significance of the lesion.
- The residual or reserve cardiac function.
- The presence of concomitant effects on the pulmonary, renal and hepatic function.

The anaesthetist should also consider the presence of coronary artery disease. Even in the absence significant coronary artery disease, patients with severe aortic stenosis or regurgitation can develop myocardial ischaemia. (2)

Congestive cardiac failure is also a frequent finding among patients with chronic valvular heart disease. (4) Cardiac failure is typically defined as the inability of the heart to produce sufficient (cardiac) output for the body's requirements and venous return. (1)

Cardiac failure can be caused by:

- Increased work load on the heart:
 - Increased **preload** (Aortic regurgitation, mitral regurgitation, atrial septal defect, ventricular septal defect, severe anaemia, fluid overload).
 - Increased **afterload** (Hypertension, pulmonary stenosis, aortic stenosis, pulmonary embolus, pulmonary hypertension).
- Decreased myocardial contraction/contractility (Myocardial infarction, ischaemic heart disease, cardiomyopathy, arrhythmia).
- Reduced filling (Tricuspid stenosis, mitral stenosis, tamponade, pericarditis, decreased ventricular compliance). (3)

Valvular heart disease, depending on the valve involved places a haemodynamic strain on the left and/or right ventricle. This strain is tolerated initially as the cardiovascular system compensates physiologically to the overload however the haemodynamic overload eventually leads to cardiac muscle dysfunction, congestive cardiac failure and potentially, sudden death.

An understanding of the underlying physiological disturbance and haemodynamic alterations that accompany these valvular lesions is important when considering the management of these patients pre- and intra-operatively. (4) The anaesthetist must plan an appropriate anaesthetic based on the physiological and haemodynamic disturbance.

Pharmacological management of these valvular lesions is aimed at altering underlying cardiac rhythm, heart rate, systemic blood pressure, systemic vascular resistance and pulmonary vascular resistance. (4)

Patient Assessment.

When evaluating patients with cardiac valvular disease (or any cardiac disease), it is useful to define the patient's exercise tolerance as a measure of cardiac reserve. (4) Several classification systems are have been or are in use:

Cardiac risk index: (3)

This is a scoring system for preoperative identification of patients at risk from major perioperative cardiovascular complications. Retrospective data from 1001 patients (age >40 years) undergoing non-cardiac surgery was collected in 1977. This proved to have high specificity (if patient is scores high, they are high risk), but low sensitivity (not all high risk patients are identified). (3) (5)

New York Heart Association classification. (3) (7)

Is a method of preoperative assessment of cardiac disease, originally used for cardiac failure.

ASA Classification: (3) (6)

ASA physical status: Classification system defined by the American Society of Anesthesiologists for assessing preoperative physical status. Not a sensitive predictor of anaesthetic mortality, but there is a reasonable correlation with overall outcome. Can produce inconsistent results between anaesthetists.

Valvular disease frequently causes an accompanying murmur. Heart murmurs are due to turbulent blood flow across an abnormal valve or cardiac orifice. Systolic murmurs may also be physiological, whereas diastolic murmurs are almost always pathological. (3) Murmurs from stenotic lesions are typically harsh. Regurgitant murmurs are typically soft. Murmurs originating from the left side of the heart are best heard in expiration, those from the right side are best heard in inspiration. (3)

Classification of murmurs: (3)

Systolic:

Pansystolic: Ventricular septal defect, Mitral Regurgitation, Tricuspid Regurgitation.

Ejection: Aortic Stenosis or Aortic sclerosis, Pulmonary Stenosis, Atrial Septal Defect.

Diastolic:

Mitral Stenosis, Atrial Regurgitation.

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VALVULAR HEART DISEASE – AORTIC STENOSIS

Background.

Aortic stenosis increases the perioperative morbidity and mortality. It increases the risk of cardiovascular complications in the perioperative period for elective, non-cardiac surgery, especially if cardiac failure and arrhythmias are present. (1)

The aortic valve sits between the left ventricle and aortic root and regulates the direction of blood flow from the left ventricle into the aortic root. If the aortic valve becomes narrowed, the flow of blood from the left ventricular outflow tract becomes impeded or obstructed causing a condition called aortic stenosis. Thus, aortic stenosis is a condition caused by the incomplete opening of the aortic valve.

When the aortic valve becomes stenosed, the obstruction to flow causes a pressure gradient to develop between the left ventricle and the aortic root. (2) The more stenosed the aortic valve, the higher the pressure gradient between the left ventricle and the aorta.

With a gradient of 30 mmHg at the peak of systole, the left ventricle may generate a pressure of 140 mmHg but the pressure that is transmitted to the aorta will only be 110 mmHg. Thus, a non-invasive blood pressure cuff may indicate a normal systolic blood pressure, when the actual pressure generated by the left ventricle would be considerably higher. (3)

Anatomical obstruction to the left ventricular outflow leads to concentric hypertrophy of the ventricle muscle that eventually results in decreased diastolic compliance. (4) Long standing aortic stenosis causes hypertrophy of the left ventricle but with no increase in the left ventricular end-diastolic volume and a stiff or non-compliant ventricle with decreased diastolic function (impaired relaxation). This leads to a higher oxygen demand of the ventricle along with higher filling pressures to maintain the stroke volume. Eventually the left ventricle fails with an increase in the left ventricular diastolic pressure (LVEDP) that can lead to mitral regurgitation and increased pulmonary artery pressures. With this situation (high pulmonary artery pressure), the right ventricle can also begin to fail. (5)

The natural history of aortic stenosis in the adult population consists of an extended latent period where the morbidity and mortality are relatively low. (5) Once symptoms start to develop, a significant point has been reached in the natural history of aortic stenosis. As already mentioned, severe aortic stenosis is a risk factor for perioperative cardiac complications in non-cardiac surgery. (1) If the patient also has coexisting cardiac failure or a dysrhythmia, the risk is significantly increased.

Incidence and Causes.

Aortic stenosis (AS) is most commonly a degenerative disease that is increasing as life expectancy is increasing and the population is ageing. Other causes are usually either congenital, or rheumatic in aetiology (See diagram 1).

AS is the most common cardiac valve abnormality in the United States, regardless of whether congenital or acquired in aetiology. The incidence at post-mortem is approximately 1%. The incidence at birth (congenital aortic stenosis) is approximately 0.1%. (1) (6)

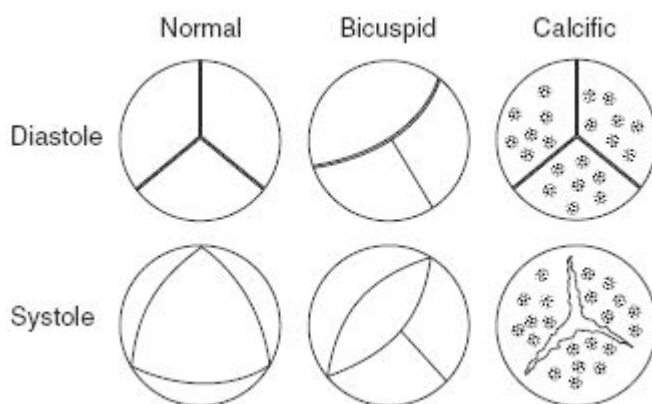
Aortic sclerosis (irregular thickening of the aortic valve without left ventricular obstruction) is present in approximately 25% of people over the age of 65 years. (6)

Degenerative calcific aortic stenosis is the most common cause of AS (at least in the United Kingdom), tending to occur in patients that are aged greater than 70 years. Over time, mechanical stress forces cause fibrosis and also calcification of the valve to form, even on a previously normal valve with the normal number of cusps (3). Some sources now state that the process is more typical of an inflammatory process rather than degeneration, similar to the pathogenesis of atherosclerosis in blood vessels. (6) (7) The first phase of this degenerative process has been termed ‘aortic sclerosis’ and the thickened valve cusps do not cause any obstruction to flow through to the aortic root. (1) Eventually, the disease process causes a reduction in cusp/leaflet movement. (6) This form of the disease is usually seen in the later decades of life. (2)

Of the congenital cardiac malformations, a bicuspid rather than tricuspid (normal) aortic valve is the commonest, occurring in up to 2% of the population. There is a male > female predominance. The abnormal number of valve cusps leads to turbulence of flow across the valve. The turbulent flow leads to valve trauma (endothelial damage), leading to inflammation and eventually produces fibrosis, calcification and stenosis. Bicuspid valves are also prone to regurgitation and infection (endocarditis). Although present at birth, this form of the disease does not usually present until the middle decades of life. (1) (7)

Rheumatic disease causing stenosis of the aortic valve is rarely isolated to the aortic valve. It can also be commonly associated with aortic incompetence/regurgitation or mitral valve disease.

Diagram 1: Variation in aortic valve anatomy seen in 2D-echocardiography. (1)



Taken from: Brown J, Morgan-Hughes NJ. Aortic stenosis and non-cardiac surgery. Continuing Education in Anaesthesia, Critical Care and Pain. Volume 5, No.1 2005.

Physiology and Pathophysiology.

Acute obstruction of the left ventricular outflow tract rapidly dilates the ventricle and significantly reduces the stroke volume. Conversely, the obstruction to left ventricular outflow caused by aortic stenosis is more insidious in onset, occurring gradually. This allows the ventricle to compensate and maintain the stroke volume (initially). Obstruction to the ejection of blood from the left ventricle into the aorta due to a decrease in the area of the aortic valve orifice requires an increase in the left ventricular pressures to maintain the stroke volume, producing a pressure gradient between the left ventricle and aortic root (See diagrams 2 and 3). (7)

The normal aortic valve is comprised of 3 cusps with a valve area of 2.6 to 3.5 cm². Haemodynamically significant obstruction to left ventricular output occurs as the aortic valve area approaches 1cm². (1)

With gradual onset of aortic valve obstruction the left ventricle (LV) is required to generate greater intraventricular pressures to eject the same stroke volume (i.e. there is a greater afterload to overcome). LV output is maintained secondarily to hypertrophy of the left ventricle as it adapts to the systolic pressure overload. Left ventricular wall thickness increases but the normal ventricular chamber volume is maintained. Hypertrophy allows the ventricle to maintain a pressure gradient across the aortic valve without the ventricle dilating or reducing the cardiac output. (6)

The stroke volume is maintained due to this concentric ventricular hypertrophy which allows the ventricle to generate a significant transvalvular gradient and reduce the ventricular wall stress (afterload). (4) Concentric hypertrophy is thus a response to increased intraventricular pressure. Hypertrophy of the left ventricle (i.e. increased ventricular wall thickness) in the setting of an increased left ventricular pressure maintains the left ventricular wall tension at near normal values, according to the Law of Laplace. (7) $\text{Wall tension} = [\text{Pressure} \times \text{Radius}] / [\text{Wall thickness} \times 2]$

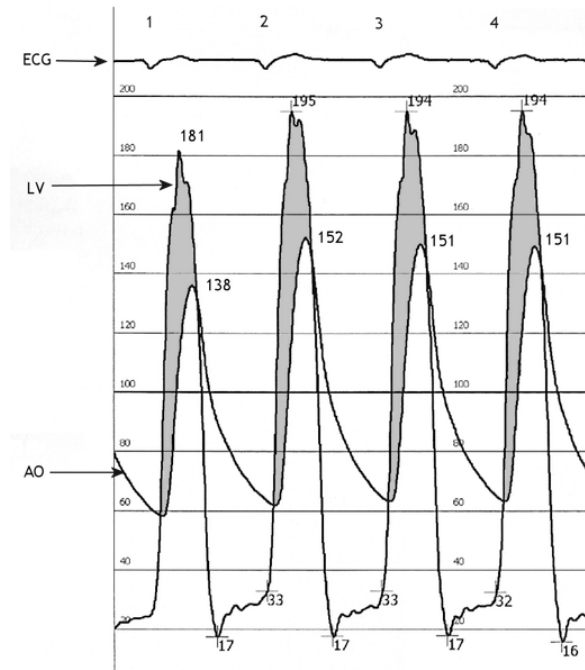
Due to these compensatory mechanisms, LV output can be maintained for several years without producing dilatation of the ventricle or causing symptoms. This hypertrophy response is an appropriate and beneficial response to compensate for increases in intraventricular pressures. But it does have some adverse effects as well. The hypertrophied ventricle may have reduced coronary blood flow. With exercise or tachycardia, there may be a maldistribution of coronary blood flow leading to subendocardial ischaemia which can further contribute to both systolic and diastolic dysfunction. Increased sensitivity to ischaemic injury (with larger infarcts) due to the larger cardiac muscle mass. (6)

As the left ventricle becomes more and more hypertrophied, it becomes as a consequence less compliant (or stiff) causing diastolic dysfunction (impaired relaxation). This can be seen with an increase in the left ventricular end-diastolic pressure (LVEDP). Decreased compliance means the ventricle is more difficult to fill (the intraventricular pressure increases with a smaller increase in volume). When this situation arises, the ventricle is increasingly dependent on atrial contraction for ventricular filling (passive filling is reduced secondary to decreased compliance and subsequent increases in LVEDP). The left atrium hypertrophies as a consequence to maintain ventricular filling which can leave it susceptible to arrhythmias. At this point, if the patient loses

their sinus rhythm (for example atrial fibrillation or flutter), symptoms may develop. Normally, atrial contraction contributes approximately 20 or 30% of the ventricular filling (preload). In patients with aortic stenosis, atrial contraction is more important, contributing up to 30 or 40% of ventricular filling (as the ventricle is less compliant).

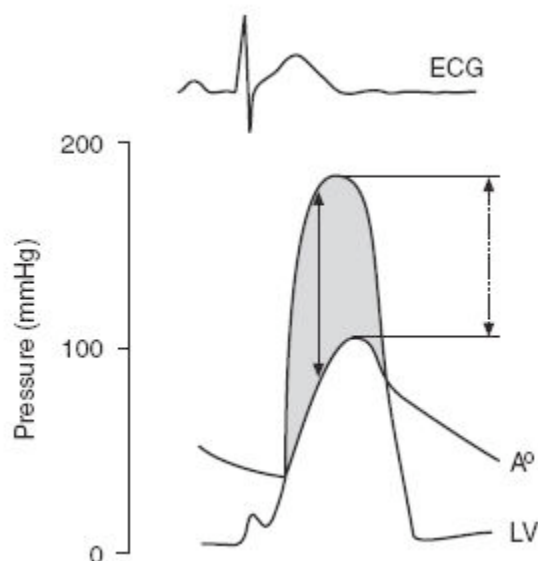
Another long term consequence of chronic aortic stenosis is a depression of the myocardial contractility. This further contributes to a deterioration of the left ventricular function. (4)

Diagram 2: Superimposed left ventricular (LV) and aortic root (Ao) pressure trace showing the gradient between the left ventricle and aortic root in aortic stenosis. (3)



Taken from: http://en.wikipedia.org/wiki/Aortic_stenosis

Diagram 3: Simultaneous left ventricular (LV) and aortic root (Ao) pressure tracings in a patient with aortic stenosis. (1)



Taken from: Brown J, Morgan-Hughes NJ. Aortic stenosis and non-cardiac surgery. Continuing Education in Anaesthesia, Critical Care and Pain. Volume 5, No.1 2005.

The myocardial oxygen demand increases secondary to ventricular hypertrophy (increased muscle mass) and increased left ventricular systolic pressures, but the myocardial oxygen supply actually decreases due to decreased aortic root pressure (and decreased coronary artery driving pressure) and compression of the intramyocardial coronary arteries. This compression is secondary to the high intraventricular pressures generated during systole. (4)

The mismatch in oxygen supply and demand is one of the reasons patients with advanced aortic stenosis develop angina (myocardial ischaemia) in the absence of coronary artery disease. (1)

Aortic stenosis is most commonly classified based on the reduction in aortic valve area and/or the corresponding pressure gradient across the valve.

Aortic valve area reduction: (5)

Normal	2.6-3.5cm ²
Mild	1.2-1.8cm ²
Moderate	0.8-1.2cm ²
Significant	0.6-0.8cm ²
Critical	<0.6cm ²

Left ventricle-aortic gradient: (5)

Mild	12-25mmHg
Moderate	25-40mmHg
Significant	40-50mmHg
Critical	>50mmHg

If using the gradient to classify the severity of the stenosis, it will underestimate the severity once the left ventricle starts to fail, as the pressure gradient will start to decrease. (1)

With significant or critical AS (i.e. valve area reduction of 0.5-0.7), the transvalvular gradient is usually 50mmHg or greater, with a normal cardiac output. These patients are unable to significantly increase their cardiac output and are said to have a relatively 'fixed' cardiac output.

Clinical manifestations and Symptoms.

Patients with aortic stenosis are often asymptomatic for several decades due to adequate physiological (and clinical) compensation. Symptoms do not often develop until after a long latent or asymptomatic period. When symptoms do develop in advanced aortic stenosis, patients present with a classic triad of: (4) (7)

Myocardial ischaemia (Angina)

Pulmonary congestion (Dyspnoea on exertion)

Inadequate cerebral perfusion (Orthostatic/exertional syncope)

The onset of symptoms has significant prognostic consequences or implications. If the patient develops angina (myocardial ischaemia), the 5-year survival rate is less than 50% in the absence of surgery (aortic valve replacement). If the patient develops syncope and/or dyspnoea the prognosis is worse. With syncope only 50% of patients will be alive at 3 years. Dyspnoea carries a grave prognosis with only 50% alive at 2 years. (7)

Diagnosis.

Aortic stenosis can be diagnosed when the patient is asymptomatic, such as during a routine examination of the cardiovascular system. Classic signs include a plateau pulse (slow rising, sustained upstroke, low volume with reduced pulse pressure) and an ejection systolic murmur (which radiates to the neck (carotid arteries) and is loudest in the aortic area when the patient is leaning forward in expiration). In severe aortic stenosis, the murmur may be less prominent, especially as the left ventricle begins to fail. An apical thrill may also be palpable.

Investigations.

ECG findings:

The ECG may show non-specific changes. Left ventricular hypertrophy may be evident in 85% of patients with severe aortic stenosis. There may be a left ventricular strain pattern.

CXR findings:

A CXR may show cardiomegaly or signs of pulmonary oedema or a calcified aortic annulus.

Echocardiography:

If available can be used to determine and assess the anatomy of the aortic valve as well as to calculate the gradient across the aortic valve and determine the severity of the stenosis and assess the left ventricular function.

Cardiac catheterization:

If available can also be used to determine the severity of the stenotic lesion and the left ventricular function.

Anaesthetic Implications / Treatment.

Most patients die within 2-3 years without surgical treatment (replacement of the aortic valve) once symptoms start to develop. (4) Patients with symptoms from aortic stenosis should undergo an aortic valve replacement. (7) Aortic valve replacement usually relieves the symptoms of aortic stenosis and the stroke volume/ejection fraction typically increases post-surgery. (8) However, the aortic valve area (reduction) at which symptoms typically develop is quite variable. (7)

The incidence of sudden death in patients with asymptomatic severe/critical aortic stenosis is high and quoted at 2%. (7)

Except for the use of antibiotic prophylaxis to prevent infective endocarditis, there is currently no effective specific medical treatment for aortic stenosis. (8)

In patients with aortic stenosis, the following may occur in the perioperative period:

- Myocardial ischaemia.
- Ventricular (and atrial) arrhythmias.
- Left ventricular failure. (2)

Patients with aortic stenosis are at an increased risk of perioperative cardiovascular complications, but if the condition is recognized preoperatively, non-cardiac surgery can be conducted relatively safely provided that adequate monitoring and management are in place. Patients should have a diagnostic transthoracic echocardiogram preoperatively. If not available, treat the patient as if they have at least a moderate grade of stenosis.

Careful haemodynamic monitoring is very important. Invasive arterial blood pressure measurement is employed to monitor beat-to-beat arterial blood pressure. A central venous catheter should be used as a guide to intravascular filling, and for central administration of vasoactive drugs. A pulmonary artery catheter may precipitate arrhythmias and is not necessarily recommended. (1)

Maintenance of a normal sinus rhythm, normal heart rate and adequate intravascular volume is of importance during anaesthesia. (4)

For patients with aortic stenosis undergoing elective non-cardiac surgery, management of anaesthesia should avoid situations or events that could lead to a further reduction in the cardiac output. (8)

Since regional neuraxial techniques (epidural or spinal anaesthesia) will cause blockade of the peripheral sympathetic nervous system and may produce dramatic changes in systemic vascular resistance, general anaesthesia is often preferred. Sympathetic blockade and decreased systemic vascular resistance can decrease the venous return to the heart (due to vasodilation of venules and arterioles) that can decrease the cardiac output and coronary perfusion. (8)

Limb blocks can be useful if a regional technique is desirable since the impact on sympathetic blockade is reduced compared with a neuraxial technique. They can also be used alone or combined with a general anaesthetic. (1)

However, there are reports of successful use of regional techniques using intrathecal catheters or epidurals. These blocks were titrated carefully using small boluses of anaesthetic agents. Collard et al. used a continuous spinal anaesthetic (CSA) technique in 2 patients with critical aortic stenosis undergoing lower limb surgery with good results. (8)

During anaesthesia of patients with aortic stenosis, it is very important to avoid the following situations: (1) (2) (4) (5) (8)

- Loss of normal sinus rhythm:

Because of the increased left ventricular end-diastolic pressure (LVEDP), normal atrial contraction is vital to maintaining adequate left ventricular filling (Atrial contraction can contribute up to 40% of filling).

- Peripheral vasodilation:

Since the cardiac output in these patients is relatively fixed, falls in systemic vascular resistance (peripheral vasodilatation) can not be compensated for, which may result in significant hypotension, myocardial ischaemia and a further decrease in myocardial contractility.

- Excessive peripheral vasoconstriction:

This also can also reduce left ventricular output. Afterload should be maintained as normal as possible as any decrease in diastolic pressure may lead to a reduction in coronary blood flow to the hypertrophied ventricle.

- Tachycardia

This shortens the diastolic time and will impair ventricular filling and reduce coronary blood flow. Tachycardia also increases the myocardial oxygen demand. It is important to maintain a normal or slightly lower pulse rate.

Therefore the heart rate must be normal or slow. Preload must be increased to facilitate filling of the stiffened/non-compliant ventricle and the afterload must be maintain but not excessively high to facilitate coronary blood flow. Contraction of the non-compliant ventricle can be facilitated with an adrenaline infusion if required.

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VALVULAR HEART DISEASE – AORTIC REGURGITATION.

Background (1).

Aortic regurgitation (AR) is characterized by the diastolic reflux of blood from the aorta into the left ventricle due to malcoaptation of the aortic cusps.

The aortic valve sits between the left ventricle and aortic root. With a normally functioning aortic valve, the valve only opens when the left ventricular pressure is higher than the aortic root pressure during ventricular systole. This allows the flow of ejected blood to proceed from the left ventricle into the aorta during ventricular systole. At the conclusion of ventricular systole, the ventricle relaxes (isovolumetric) and ventricular pressure decreases in preparation for diastolic filling from the left atrium. As the ventricular pressure decreases in the early phase of diastole, the pressure in the aortic root becomes higher than that of the ventricle and the aortic valve then closes. This prevents retrograde flow of blood from the aorta back into the ventricle.

The amount of blood ejected from the left ventricle during systole per heart beat is known as the stroke volume (end diastolic volume – end systolic volume). Stroke volume (SV) is related to the cardiac output (CO) and heart rate (HR) as follows: $SV = CO / HR$

The aortic valve thus regulates the direction of blood flow from the left ventricle into the aortic root. If the aortic valve becomes regurgitant or leaky (the aortic valve fails to close completely), the forward left ventricular stroke volume is decreased. This is because part of the stroke volume ejected from the left ventricle regurgitates (reverse flow) back into the left ventricle from the aortic root during ventricular diastole.

After the aortic valve closes, there is normally a short period of time when the left ventricle relaxes isovolumetrically (with no change in volume). The mitral valve is also closed at this time. If the aortic valve is regurgitant, instead of the left ventricle relaxing without a change in volume, it begins to fill from the aortic root due to incomplete aortic valve closure. This causes an increase in the left ventricular volume prior to the opening of the mitral valve (when normal ventricular filling occurs). When the mitral valve opens, the ventricle fills further from the left atrium (passively and actively). Therefore, the left ventricular preload is increased in patients with aortic regurgitation.

Thus, aortic regurgitation, a condition caused by the incomplete closure of the aortic valve due to disease of the aortic cusps or aortic root that distorts the cusps preventing their coaptation causing retrograde flow of blood from the aortic root (across the aortic incompetent aortic valve) back into the left ventricle during normal diastole. This imposes a volume (preload) overload on the left ventricle.

Aortic regurgitation can develop either acutely or chronically. Pulmonary oedema and hypotension are prominent with acute onset of AR. (4) Acute AR is a surgical emergency and has a very poor prognosis, but is a rare condition. (1)

Progressive congestive cardiac failure is the main feature of chronic onset AR. (4)

Aortic regurgitation may also be associated with aortic root dilatation (in conjunction with aortic stenosis) or aortic root dissection.

As will be discussed subsequently, aortic regurgitation produces a combined volume overload (increased preload) and pressure overload on the left ventricle. The left ventricle becomes volume overloaded and progressively dilates to compensate. In response to the increased ventricular preload, there is:

- Increased sympathetic nervous system drive that leads to tachycardia and increased myocardial contractility to maintain the cardiac output.
- Peripheral vasodilatation and
- Fluid retention to further increase the preload. (5) (6)

Aortic diastolic pressure depends on a competent aortic valve. Thus, in AR the aortic diastolic pressure decreases, which has consequences for coronary blood flow (coronary blood flow is related to the difference between the aortic end-diastolic pressure and the ventricular end-diastolic pressure). Since the aortic end-diastolic pressure is decreased and the ventricular end-diastolic pressure gradually increases with the course of the disease therefore coronary blood flow is impaired.

Incidence and Causes.

The true prevalence of chronic aortic regurgitation and the incidence of acute aortic regurgitation are presently unknown. There are reports that the overall prevalence in men is up to 13% and women 8.5%. The AR in these cases was however only mild. (1)

There are many common causes of aortic regurgitation. The majority of cases of AR are caused by aortic root dilatation. In the majority of patients, this is idiopathic but it is also associated with sustained systemic hypertension and advancing age.

Aortic regurgitation can be caused by (6):

- Aortic valve leaflet (cusp) disease.
- Rheumatic disease (mitral involvement is also very common)
- Congenital abnormalities (bicuspid valve)
- Atherosclerotic or calcific degeneration
- Infective endocarditis
- Anorectic drugs (appetite suppressants)
- Aortic root disease
- Idiopathic aortic dilatation e.g. from long standing hypertension, advanced age
- Aortic dissection (of ascending aorta)

Aortic valve abnormalities are usually either:

- Congenital in aetiology, or
- Rheumatic in nature (e.g. rheumatic fever).

The most common congenital abnormality of the aortic valve is the presence of a bicuspid (2 leaflet) valve. If a bicuspid aortic valve results in aortic regurgitation, it is also usually associated with concomitant aortic stenosis. (7)

Diseases that affect the ascending part of the aorta or aortic root cause dilatation of the aortic annulus and thus lead to aortic regurgitation. Much less commonly seen causes of aortic regurgitation are (6):

- Traumatic chest injuries, Syphilis, Annuloaortic ectasia.
- Cystic medial necrosis (+/- Marfan syndrome).
- Ankylosing spondylitis (causes disease of both the cusps and aortic root).
- Both rheumatoid and psoriatic arthritis.
- Osteogenesis imperfecta, Giant cell aortitis.
- Ehlers-Danlos syndrome and Reiter's syndrome.
- Other connective tissue disorders or collagen diseases.

Most of the listed causes of aortic regurgitation (whether common or uncommon) typically lead to an insidious onset of aortic regurgitation (chronic AR). This leads to a slow and gradual onset of left ventricular dilatation which is compensated physiologically with a long latent period in which the patient can be asymptomatic. (6) Acute onset of AR is typically caused by infective endocarditis, chest trauma or aortic dissection. It produces a severe and sudden onset of symptoms with the sudden increase in left ventricular filling pressures resulting in a marked reduction in cardiac output. (6)

Physiology and Pathophysiology.

Acute Aortic Regurgitation

In this condition, there is a sudden and large regurgitant volume imposed on the left ventricle. The ventricle is of normal size and does not have time to compensate for the increased volume (volume overloaded). The left ventricular end-diastolic pressure (LVEDP) rapidly increases (the ventricle now operates on the steep part of the Frank-Starling curve – See Diagram 1). The LVEDP and left atrial pressure markedly increase.

Diagram 1: Relationship between the stroke volume (cardiac output) and left ventricular end diastolic pressure (LVEDP). (8)

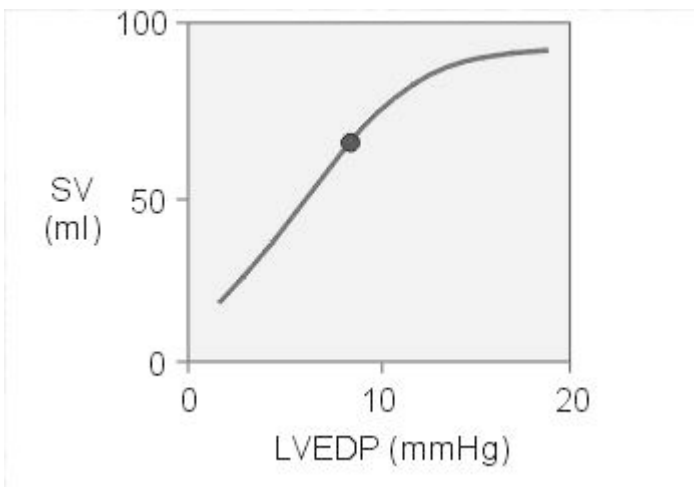


Diagram taken from: <http://www.cvphysiology.com/Cardiac%20Function/CF003.htm>

Starling's law of the heart states that the force of myocardial contraction (represented by stroke volume or cardiac output) is proportional to the initial fibre length or preload (represented by the left ventricular end-diastolic pressure).

This mechanism is in effect in acute AR, but since the ventricle has not had sufficient time to dilate the forward stroke volume is significantly decreased. Compensatory tachycardia develops in an attempt to maintain the cardiac output ($SV = CO/HR$, thus $CO = SV \times HR$)

Patients present typically with acute pulmonary oedema and cardiogenic shock and due to increased myocardial oxygen requirements, myocardial ischaemia and sudden death are common in acute and severe aortic regurgitation. (6)

Chronic Aortic Regurgitation.

In chronic AR, there is a decrease in the forward stroke volume ejected from the left ventricle since part of the stroke volume is regurgitated from the aortic root back into the ventricle during diastole. The left ventricle is subjected to a chronic volume overload.

The volume of the regurgitation is dependent on:

- The heart rate (Determines the time available for regurgitant flow).
- The pressure gradient across the aortic valve (Which depends on the systemic vascular resistance).

The volume of the regurgitation is reduced in the setting of tachycardia (less time for reverse flow) and peripheral vasodilatation (reduced afterload). (3)

With chronic AR the left ventricle undergoes progressive dilatation and eccentric hypertrophy (compared with concentric hypertrophy in aortic stenosis). The chronic volume overload from the regurgitation stimulates the ventricle to hypertrophy. This hypertrophy is an attempt to maintain the ventricular wall tension (according to the Law of Laplace).

$$\text{Wall tension} = [\text{Pressure} \times \text{Radius}] / [\text{Wall thickness} \times 2]$$

Along with eccentric hypertrophy, the ventricle undergoes a number of other compensatory mechanisms:

- Increased end-diastolic volume
 - Patients with chronic AR have the largest end-diastolic volumes of any heart disease. The resulting massive dilatation of the heart is also referred to as a cor bovinum. (4)
- Increased compliance (to enable the increased ventricular volume to be accommodated without an increase in filling pressures (LVEDP)). (6)

The increased end-diastolic volume (preload), serves to allow the ventricle to eject a larger stroke volume and thus maintain a relatively normal forward stroke volume. Note that the total stroke volume = effective stroke volume – regurgitant volume.

Due to ventricular hypertrophy and dilatation, the left ventricular function is typically normal but because of the enlarged size of the ventricle (dilated) and the concomitant increase in wall stress or tension, there is an increase in the left ventricular afterload (greater wall tension is required to produce the necessary pressure to eject the larger stroke volume). The increased afterload also stimulates the ventricle to hypertrophy. This is seen as concentric hypertrophy (similar to aortic stenosis).

As previously mentioned, chronic aortic regurgitation results in a volume overload of the left ventricle, however due to the increased left ventricular afterload. There is also a pressure overload. (6) The pressure overload is due to systolic hypertension that occurs due to the increased total aortic (ventricular) stroke volume. This is because the previous regurgitant volume and the forward stroke volume are ejected into the aorta during systole. (1)

Eventually, ventricular function deteriorates, as the compensatory mechanisms can no longer cope with the volume and pressure overload. The stroke volume or ejection fraction decrease. The left ventricular end-diastolic pressure and volumes rise. This transmits to the pulmonary circulation leading to pulmonary hypertension and pulmonary oedema. Decreased coronary blood flow due to decreased diastolic pressure can lead to myocardial ischaemia (in the absence of coronary artery disease). (6)

Clinical manifestations and Symptoms.

Many patients with severe chronic aortic regurgitation may remain asymptomatic and clinically compensated for many years or decades (10-30 years) with normal left ventricular function. Symptoms typically occur once significant cardiomegaly and myocardial dysfunction have developed. (3) (7)

If the regurgitant volume is less than 40% of the stroke volume, symptoms are typically minimal in chronic aortic regurgitation. If the regurgitant volume becomes greater than 60% of the stroke volume, symptoms are generally more severe. (4)

When symptoms do develop in advanced aortic regurgitation, patients generally present with (7):

- Dyspnoea and especially exertional dyspnoea secondary to pulmonary congestion.
- Orthopnoea and paroxysmal nocturnal dyspnoea.
- Fatigue reflecting reduced forward stroke volume
- Angina (Although not common, usually occurs during sleep when the patient's heart rate decreases and can occur even without coronary artery disease.

In contrast to aortic stenosis, sudden death from aortic regurgitation is a rarer event. (3)

Due to inability of the left ventricle to cope with sudden increase in volume in acute aortic regurgitation, patients often develop sudden and severe dyspnoea and hypotension.

Diagnosis.

As discussed under the Physiology and Pathophysiology section – Aortic regurgitation produces a wide pulse pressure and a marked decrease in aortic diastolic blood pressure. This is responsible for the peripheral physical signs seen in patients with aortic regurgitation.

Physical findings in chronic aortic regurgitation an early diastolic murmur which is high pitched, loudest in expiration and leaning forward typically heard over left sternal edge at the 3rd and 4th interspaces. There may also be a systolic ejection murmur due to the ejection of high volumes of blood as well as an Austin-Flint murmur heard in mid-diastole due to the regurgitated flow hitting the closed mitral valve.

The pulse is described as “Water hammer” pulse which is a collapsing pulse with widened pulse pressure. Other pulse related signs include; Corrigan's sign (a bounding carotid pulse), Muller's sign (a pulsating uvula), de Musset's (head bobbing) and Quincke's sign (visible capillary pulsations in nail bed).

Patient may also demonstrate signs of left ventricular failure.

Investigations.

ECG

The ECG may show non-specific changes with left ventricular hypertrophy and a left ventricular strain pattern. In the limb leads the ST-T changes occur opposite the main QRS forces.

CXR

May show cardiomegaly (left ventricular dilatation) or signs of pulmonary oedema The heart may appear “boot-shaped”. (5)

Echocardiography

This is the most important diagnostic test for the evaluation of AR.

If available, echocardiography can be used to determine and assess the anatomy of the aortic valve leaflets and aortic root and determine the presence of AR and calculate the regurgitant fraction (severity) as well as assessing left ventricular size and function.

Cardiac catheterisation.

If available, cardiac catheterization, can also be used to determine the severity of the regurgitant lesion and the left ventricular function. It is also useful to determine the coronary anatomy in patients that require aortic valve replacement. (1)

Anaesthetic Implications/Treatment.

The important prognostic and management variables in patients with aortic regurgitation are (7):

- Presence (or absence) of symptoms.
- Assessment of left ventricular function:
- Either by echocardiography or cardiac catheterization.

Asymptomatic patients can generally tolerate non-cardiac surgery very well. (5)

Most sources agree that in symptomatic patients, with severe aortic regurgitation, aortic valve replacement surgery should be offered. (6) (7)

Treatment of Aortic regurgitation is based on:

- The suddenness of presentation
- Degree of signs or symptoms
- Degree of left ventricular systolic or diastolic dysfunction

Treatment is generally either medical or surgical in nature.

Medical treatment.

Medical management is usually pursued for asymptomatic patients with normal left ventricular function in conjunction with regular monitoring and surveillance. (7)

The main goal of medical therapy is to reduce the systolic hypertension associated with chronic severe aortic regurgitation. (1)

Medical management aims to decrease the systolic hypertension and thereby reducing the left ventricular afterload (and improve the afterload mismatch that stresses the left ventricle). Vasodilators such as hydralazine and nifedipine have received attention in various studies and have been useful in delaying the need for surgery. (1) Vasodilators improve the forward stroke volume and reduce the regurgitant volume. (6)

Cardiac glycosides (e.g. digoxin), salt-restricted diets and diuretic agents (such as ACE inhibitors) are also commonly used.

May also benefit patients with severe regurgitation that are not suitable candidates for surgical replacement of the aortic valve. (1)

Patients that develop acute/severe aortic regurgitation usually require intravenous inotropic and vasodilator support before urgent surgery is undertaken. (4)

Surgical treatment.

Surgical replacement of the aortic valve before permanent left ventricular dysfunction occurs is recommended, in both symptomatic and asymptomatic patients. (3) The operative mortality is quoted at approximately 4% for an isolated aortic valve replacement. (1) It is higher if there is coexisting aortic root disease.

The AHA currently recommends aortic valve replacement (6):

- For symptomatic patients with severe regurgitation, irrespective of left ventricular systolic function.
- For asymptomatic patients with chronic severe regurgitation and left ventricular systolic dysfunction at rest (ejection fraction <50% or left ventricular end-systolic dimension >55mm).

Anaesthetic goals (2) (3) (5).

Patients with asymptomatic aortic regurgitation that require minor non-cardiac surgery probably do not require full invasive haemodynamic monitoring. (3)

In acute regurgitation or chronic severe regurgitation, full haemodynamic monitoring (if available) should be considered including invasive blood pressure, central venous pressure, pulmonary artery catheter and transoesophageal echocardiography monitoring.

The general aims of anaesthesia should be to maintain a forward left ventricular stroke volume. (93) This can be achieved by maintaining a normal to high heart rate, adequate volume loading to maintain ventricular preload, low systemic vascular resistance to facilitate forward ejection of the stroke volume and maintain myocardial contractility.

Bradycardia increases the amount of time the ventricular spends in diastole and allows the regurgitant volume to increase and worsens the ventricular volume overload.

An abrupt increase in the systemic vascular resistance (SVR) can lead to left ventricular failure. Anaesthesia generally lowers the SVR which decreases the regurgitant volume and facilitates forward flow of the stroke volume. Vasodilators can be used to reduce the SVR but excessive reduction can lead to decrease in venous return, preload and diastolic pressure (impairing coronary blood flow).

Antibiotic prophylaxis should be administered to prevent the development of infective endocarditis.

Although general anaesthesia is the most common choice for patients with aortic regurgitation, neuraxial techniques (spinal and epidural) are well tolerated. (5)

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VALVULAR HEART DISEASE – MITRAL STENOSIS.

Background.

The mitral valve sits between the left atrium and the left ventricle and regulates blood flow between these two chambers of the heart. If the mitral valve becomes narrowed, the flow of blood from the left atrium into the left ventricle becomes impeded resulting in a condition called mitral stenosis (MS).

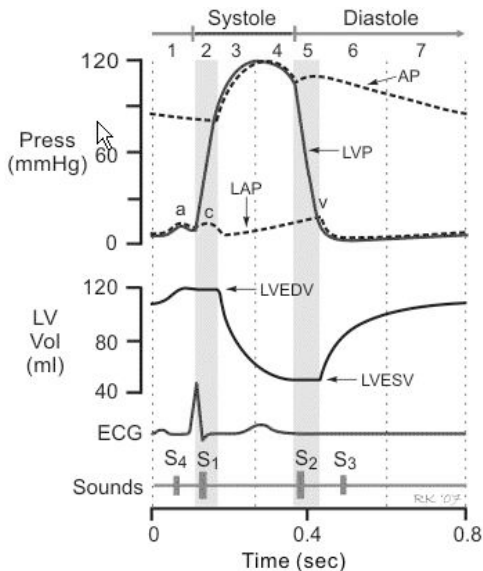
During left ventricular diastole, as the ventricle relaxes the pressure inside the ventricle falls below that of the left atrium. At this point, the mitral valve opens and allows blood to flow passively from the left atrium into the left ventricle along a very small pressure gradient. Following this passive diastolic filling of the ventricle, the left atrium contracts (to start the cardiac cycle again – see below and diagram 1) to provide the remainder of ventricular filling.

In patients with mitral stenosis the mitral valve does not completely open. As a result, the left atrium needs to generate a higher than normal pressure to eject blood into the left ventricle across the stenosed mitral valve.

The cardiac cycle is generally divided into 5 phases:

1. Atrial contraction. Contributes 30% of ventricular filling.
2. Isometric ventricular contraction (from the closing of tricuspid and mitral valves until the opening of the aortic and pulmonary valves ,when the ventricular pressures exceed the aortic and pulmonary artery pressures respectively).
3. Ventricular ejection. Lasts until the ventricular pressure falls below the aortic and pulmonary artery pressures and the aortic and pulmonary valves close.
4. Isometric ventricular relaxation. Lasts until the mitral and tricuspid valves open.
5. Passive ventricular filling. Most rapid at the start of diastole. (1)

Diagram 1: Normal Cardiac Cycle. LAP = left atrial pressure. LVP = left ventricular pressure. LVEDV = left ventricular end-diastolic volume. LVESV = left ventricular end-systolic volume. AP = aortic pressure.(2)



Taken from: <http://www.cvphysiology.com/Heart%20Disease/HD002.htm>.(2)

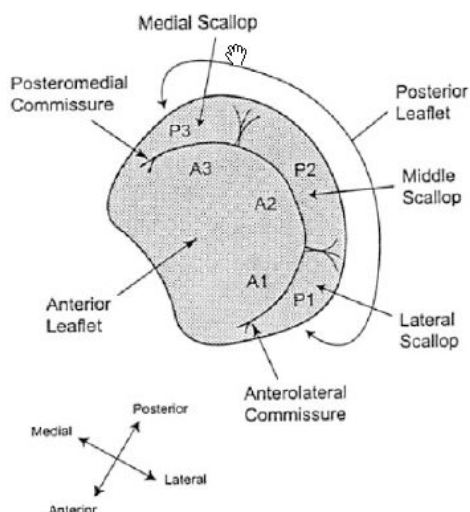
The normal mitral valve has been considered to consist of five separate components that work as a functional unit. (3)

1. Mitral valve annulus. A fibrous ring surrounding the mitral valve opening.
2. Valve leaflets.
3. Chordae tendinae. These inelastic fibres are attached from one end of the papillary muscles to the valve cusps and prevent the valve from prolapsing into the left atrium during ventricular contraction.
4. Papillary muscles which are muscle projections arising from the ventricular wall that contract during ventricular systole and work with chordae tendinae to prevent valve prolapse.
5. Immediate underlying left ventricular wall.

The normal mitral valve comprises two leaflets or cusps (bicuspid) which are asymmetrical:

- Anteromedial leaflet that comprises two-thirds of the valve but only one-third of the circumference (see diagram 2). (3)
- Posterolateral leaflet that comprises two-thirds of the circumference. This part of the valve consists of 3 scalloped areas (see diagram 2).

Diagram 2: Normal mitral valve anatomy.(3)



Taken from: Looney Y, Quinton P. Mitral Valve Surgery. Continuing Education in Anaesthesia, Critical Care and Pain. Volume 5, Number 6 2005. (3)

The normal mitral valve area is 4-6cm² (3,4,5,6). Normally symptoms do not develop until the valve area has narrowed to 2.5cm² or less. (4)

Mitral stenosis is defined as a valve area of less than 2cm². (3) Mitral stenosis is defined as severe if the valve area is less than 1cm². (3)

Table 1: Degrees of mitral stenosis.(7)

Degree of stenosis	Valve area (cm ²)	Mean gradient (mmHg)
Normal	4-6	Insignificant
Mild	>1.8	2-4
Moderate	1.2-1.6	4-9
Moderate to Severe	1.0-1.2	10-15
Severe/Critical	<1.0	>15

Adapted from: Carabello BA. Modern Management of Mitral Stenosis. Circulation 2005; 112; 432-437.(7)

Patients may remain asymptomatic for 20-30 years following the onset of the stenotic process. (6) The valve can narrow to less than 2.5cm² before the onset of symptoms. (4) If the valve area is >1.5cm², the patient may be symptomatic on exertion but not typically at rest. (4)

Symptoms may be precipitated by any condition that increases the flow of blood across the mitral valve, such as exercise, stress, infection, pregnancy and atrial fibrillation (with a rapid ventricular response). (4)

As the stenotic lesion progresses and the degree of stenosis becomes severe or critical, the patient will usually be symptomatic at rest. (4)

As quoted by the AHA “Mitral stenosis is a continuous, progressive and lifelong disease. It usually consists of a slow, stable course in the early years with a progressive acceleration of the disease later in life. Patients that are asymptomatic or minimally symptomatic, the 10-year survival rate is in the order of 80%. When the patient develops significant or limiting symptoms of mitral stenosis, the 10-year survival rate is quoted as between 0-15%. If severe pulmonary hypertension has also developed, the quoted mean survival is only 3 years. (4)

Incidence and Causes.

The majority of cases of mitral stenosis are as a delayed complication of acute rheumatic fever. (4,6,8) In all patients presenting with rheumatic heart disease, 40% have isolated mitral stenosis. (4) However, as the incidence of rheumatic fever has declined worldwide, it has led to a decreased incidence of mitral stenosis. (7) As a result, mitral stenosis is now a rare condition in developed countries. (7)

Acute rheumatic fever causes inflammation and generally causes a pan-carditis affecting the myocardium, endocardium and pericardium (7), however the long term complications are limited to the valves and endocardium. Rheumatic fever causes mitral valve leaflet thickening and calcification, fusion of the chordae tendinae or commissural fusion. (4) (5) Chronic inflammation of the valve can occur for many years after the initial acute attack of rheumatic fever. (7) It takes approximately 2 years from the diagnosis of rheumatic fever to the development of mitral stenosis. (5) It then takes up to 2 decades from patients to become symptomatic from the mitral stenosis. (5)

Other causes include congenital disease (of the mitral valve), infective and inflammatory. Congenital malformation of the mitral valve is rare and is mainly seen in infants/children. (4) Occasionally, acquired cause (left atrial myxoma, ball valve thrombus, and severe annular calcifications) of mitral valve obstruction are seen, but are rare.

If left untreated, severe mitral stenosis can lead to progressive increases in left atrial pressure, pulmonary circulation pressures and left atrial size (with an elevation of the left main bronchus). It can also result in atrial fibrillation, thrombus formation in the left atrium and obstructive changes in the pulmonary vasculature that causes failure of the right ventricle. (5)

Physiology and Pathophysiology.

Since the normal mitral valve orifice is large ($4-6\text{cm}^2$), in diastole when the mitral valve opens a common chamber is created between the left atrium and ventricle. A very small pressure gradient between the left atrium and ventricle exists very early in diastole that favours the flow of blood

from the left atrium into the ventricle (see diagram 1). This pressure gradient then dissipates and the filling pressures (in diastole) in the left atrium and ventricle are similar (if not the same). (7) A normal mitral valve will thus not impede the flow of blood from the left atrium to the left ventricle in diastole.

Mitral stenosis leads to obstruction of left ventricular inflow at the level of the mitral valve during diastolic filling of the left ventricle. (4) The reduction in valve area restricts the free flow of blood from the left atrium to the left ventricle. (4,7) A pressure gradient then develops between the left atrium and ventricle since the left atrium needs to generate a greater pressure to eject blood into the ventricle. (7) The valvular obstruction (and pressure gradient) produces progressive increases in the left atrial volumes and pressures. (6) This is because the pressure gradient is added on to the left ventricular end-diastolic pressure (LVEDP - which is normally ~5mmHg). As the valve orifice becomes more and more narrowed a higher left atrial pressure will be required to propel blood into the ventricle. With severe or critical stenosis (valve area <math><1\text{cm}^2</math>), a transvalvular pressure of about 20mmHg is required to maintain a satisfactory cardiac output. (5,8) Thus, if the LVEDP is 5mmHg, then the atrial pressure is 25mmHg. This increased atrial pressure is transmitted back to the pulmonary circulation.

Blood flow from the left atrium to the left ventricle can occur only when it is driven by a pressure gradient. The transvalvular gradient that develops is dependent on:

- Cardiac output
- Heart rate (time spent in diastole)
- Heart rhythm (presence or absence of the atrial kick component of ventricular filling). (5)

In mitral stenosis the transvalvular gradient results in an increase in the left atrial pressure resulting in increased pressure in the pulmonary venous circulation, and a markedly dilated left atrium that predisposes to various supraventricular tachyarrhythmia, especially atrial fibrillation.

The increase in the pulmonary venous circulation leads to distension of the pulmonary veins and capillaries. A critical pressure of 25mmHg in the pulmonary capillaries causes transudation of capillary fluid that leads to pulmonary oedema. (6)

As the degree of stenosis becomes critical, the diastolic filling of the left ventricle becomes significantly restricted. (7) The restricted filling reduces the left ventricular output leading to further increases in the left atrial pressure and contributing to pulmonary congestion. This pulmonary congestion and decreased cardiac output (reduced ventricular output) can mimic left ventricular failure. However, it is thought that the myocardial contractility in mitral stenosis remains relatively normal. (7)

With critical stenosis the left ventricle becomes reliant or dependent on the atrial kick component of filling in diastole however, the dilated left atrium becomes prone to tachyarrhythmia such as atrial fibrillation. As many as 50% of patients with mitral stenosis are in atrial fibrillation. (1) If the patients underlying rhythm changes from sinus to atrial fibrillation, ventricular filling can become seriously compromised with a precipitous onset of symptoms. (5)

The transudation of fluid into the pulmonary interstitium leads to decreased compliance of the lungs that causes an increase in the work of breathing leading to exertional dyspnoea. (8)

If the pulmonary congestion occurs gradually, several adaptive processes prevent overt pulmonary oedema including increased pulmonary lymphatic drainage and basement membranes thicken to tolerate the higher pulmonary venous pressure.

Although the left atrium is responsible for pumping blood across the stenosed mitral valve, it is ultimately the right ventricle that is responsible for driving blood across the pulmonary circulation into the left atrium. Thus, mitral stenosis will also cause pressure overload of the right ventricle. In severe mitral stenosis, right heart failure may develop due to the combination of left atrial pressure overload, pulmonary circulation overload and hypertension (due to hypoxic pulmonary vasoconstriction and autoregulation). (7)

Clinical manifestations and Symptoms.

Patients may be asymptomatic and present with abnormal signs on physical examination as discussed below.

Patients that have symptomatic mitral stenosis generally have:

- Exertional dyspnoea
- +/- fatigue
- Orthopnoea
- Paroxysmal nocturnal dyspnoea.
- Overt pulmonary oedema

Some patients initially present with atrial fibrillation or a thrombo-embolic event (such as a transient ischaemic attack or stroke). (4)

Although symptoms reflect left ventricular failure - left ventricular contractility is often preserved in mitral stenosis. The symptoms are as a result of pulmonary congestion due to a buildup of pressure in the left atrium (which is transmitted to the pulmonary circulation) secondary to restricted left ventricular filling in diastole.

It can take up to 20-40 years from the onset of acute rheumatic fever to the onset of symptoms caused by the ensuing mitral stenosis. Once symptoms have developed, it may take a further 10 years for the symptoms to become disabling to the patient. (4)

Diagnosis.

Diagnosis of patients with mitral stenosis is based on assessment of history, examination, CXR and ECG findings.

Pre cordial auscultation may reveal a tapping apex beat, accentuated first heart sound with an opening snap (if in sinus rhythm) and a low-pitched mid-diastolic rumble. Other findings on

clinical examination include a “mitral facies” (malar flush on cheeks), peripheral cyanosis and signs of right heart failure (raised JVP, peripheral oedema, ascites, hepatomegaly) secondary to pulmonary hypertension and right ventricular overload. (9)

Investigations.

ECG.

The ECG may show non-specific changes. If the patient is in sinus rhythm, P mitrale due to left atrial enlargement may be seen (biphasic P-wave). (8,9) Atrial fibrillation is commonly seen.

CXR .

The chest Xray may demonstrate a large left atrium, especially on a lateral film. (9) This may cause a widening of the carinal angle (splayed carina). If calcified the mitral valve will be evident. Pulmonary congestion/oedema may be present.

Echocardiography.

Echocardiography is the best non-invasive tool (and diagnostic tool of choice) used to assess mitral stenosis. (4,9) If available can be used to diagnose mitral stenosis, assess the haemodynamic conditions, assess for other valve abnormalities and assess the left ventricular function.

Management.

The major physiological problem in mitral stenosis is a mechanical obstruction to left ventricular inflow at the level of the mitral valve. No medical therapies will specifically treat or relieve the obstruction. Beta-blockers or calcium channel blockers may be useful in patients with exertional symptoms (if they are in sinus rhythm). Atrial fibrillation requires rate or rhythm control. The overall risk of systemic embolisation is age related and also related to the presence of atrial fibrillation. Embolisation (systemic) is quoted to occur in up to 10-20% of patients with mitral stenosis. (4)

Patients with mitral stenosis and chronic atrial fibrillation should be warfarinised to a target INR of 2.5 – 3.5.(7)

Surgical correction of the mitral valve is indicated when symptoms increase or pulmonary hypertension develops. Percutaneous balloon valvuloplasty can improve symptoms and delay the need for surgical replacement of the mitral valve and may be considered in selected young patients with mild to moderate mitral stenosis or patients that are a poor risk for open surgery. (4) This procedure is associated with a degree of mitral regurgitation and thrombo-embolism. (5)

Surgical replacement of the mitral valve is indicated with symptomatic patients with moderate to severe mitral stenosis.

Anaesthesia.

Basic management for patients with mitral stenosis that need non-cardiac surgery is aimed at avoiding events that are likely to decrease the cardiac output. Prophylactic antibiotics should be administered to prevent endocarditis.

The anaesthetic should aim to maintain:

- Normal to low heart rate. (Tachycardia should be treated aggressively as this will lead to decreased ventricular filling time. Beta-blocking agents such as esmolol or metoprolol are suitable. (6)
- Sinus rhythm. (Atrial fibrillation (with a rapid ventricular rate) will decrease the cardiac output).
- Preload should be adequate. (Decreased preload with decrease atrial and thus ventricular filling. Overfilling may precipitate pulmonary oedema).
- Normal to high systemic vascular resistance (SVR). (Sudden decreases in SVR are not usually well tolerated since cardiac output can only be maintained by an increase in heart rate (which decreases ventricular filling time as mentioned above).
- Avoid pulmonary hypertension. (Avoid hypercarbia, acidosis and hypoxia). (9)

Nitrous oxide should be used with caution as it can produce pulmonary hypertension. (6)

The extent of haemodynamic monitoring depends on the complexity of the surgery and magnitude of physiological disturbance to the patient. (8)

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VALVULAR HEART DISEASE – MITRAL REGURGITATION

Background.

Mitral regurgitation (MR) or mitral insufficiency, is most commonly due to rheumatic fever, and mitral stenosis usually coexists. (1,2)

Mitral regurgitation can present in an acute and severe fashion or may be slowly progressive and worsen over time, i.e. chronic mitral regurgitation. Acute and chronic mitral regurgitation tend to have different aetiologies and the clinical manifestations are significantly different. (3) Isolated or pure MR (without mitral stenosis) often presents in the acute setting. (1)

The mitral valve sits between the left atrium and the left ventricle and regulates blood flow between these two chambers of the heart. If the mitral valve becomes regurgitant or leaky, the forward stroke volume from the left ventricle is decreased as part of the stroke volume is regurgitated across the mitral valve back into the left atrium. Thus, mitral regurgitation is a condition caused by the failure of the mitral valve to close correctly.

During left ventricular systole, as the ventricle contracts the pressure inside the ventricle rises above that of the left atrium and aortic root. At this point, the mitral valve closes, abruptly stopping blood flow from the left atrium to the left ventricle. The aortic valve also opens and the stroke volume is ejected into the aortic root during the rapid and reduced ejection phase of systole. The ventricle then relaxes in diastole and the cardiac cycle starts again (see below and diagram 1).

In patients with mitral regurgitation the mitral valve does not close completely. As a result, part of the forward stroke volume that would normally pass across the aortic valve and enter the aortic root is ejected across the incompetent mitral valve into the left atrium. This imposes a volume overload on the left atrium and left ventricle (see physiology section). (3) Before the aortic valve opens in ventricular systole, as much as 50% of the left ventricular stroke volume flows into the dilated left atrium across the regurgitant mitral valve. (4) The left ventricular ejection fraction is thus reduced. A back-pressure effect occurs producing pulmonary congestion and oedema and pulmonary hypertension. (4)

The regurgitant fraction (regurgitant volume) is determined by: (4)

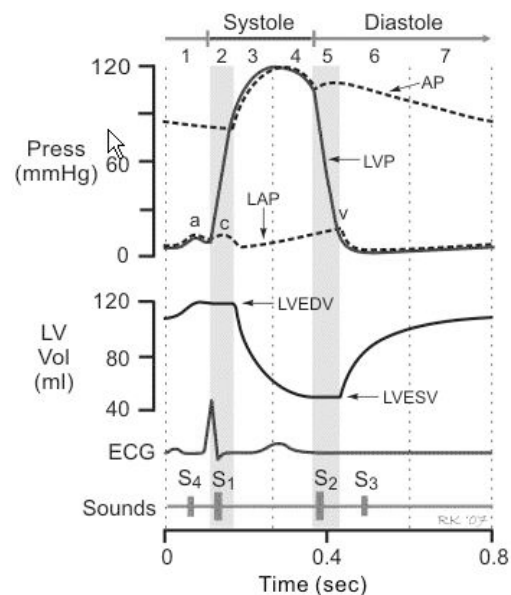
- The ventricular afterload.
- The regurgitant orifice size (varies with the ventricular chamber size). (5)
- The heart rate (or systolic time). (5)
- The pressure gradient across the mitral valve (between the left atrium and left ventricle).(5)
This depends on left ventricular compliance and impedance to left ventricular ejection into the aortic root (afterload).(1)

The cardiac cycle is generally divided into 5 phases: (2)

1. Atrial contraction. (Contributes 30% of ventricular filling).

2. Isometric ventricular contraction. (From closing of tricuspid and mitral valves until the opening of the aortic and pulmonary valves, when the ventricular pressures exceed the aortic and pulmonary artery pressures respectively).
3. Ventricular ejection. (Lasts until the ventricular pressure falls below the aortic and pulmonary artery pressures and the aortic and pulmonary valves close. It has an initial rapid phase followed by a reduced phase)
4. Isometric ventricular relaxation (Lasts until the mitral and tricuspid valves open).
5. Passive ventricular filling. (Most rapid at the start of diastole. Again with a rapid and reduced phase).

Diagram 1: Normal Cardiac Cycle. LAP = left atrial pressure. LVP = left ventricular pressure. LVEDV = left ventricular end-diastolic volume. LVESV = left ventricular end-systolic volume. AP = aortic pressure. (6)



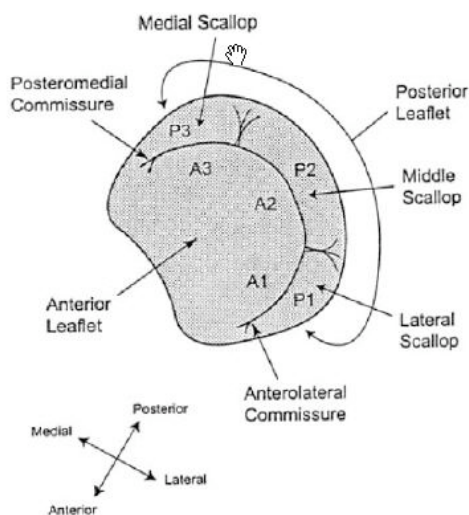
Taken from: <http://www.cvphysiology.com/Heart%20Disease/HD002.htm>.(6)

The normal mitral valve is considered to consist of five separate components that work as a functional unit. (7)

1. Mitral valve annulus. (A fibrous ring surrounding the mitral valve opening).
2. Valve leaflets.
3. Chordae tendinae. (These inelastic fibres are attached from one end of the papillary muscles to the valve cusps and prevent the valve from prolapsing into the left atrium during ventricular contraction).
4. Papillary muscles. (These muscle projections arise from the ventricular wall and contract during ventricular systole and work with chordae tendinae to prevent valve prolapse).
5. The immediate underlying left ventricular wall.

The normal mitral valve comprises two leaflets or cusps (bicuspid) which are asymmetrical. The anteromedial leaflet comprises two-thirds of the valve but only one-third of the circumference. The posterolateral leaflet comprises two-thirds of the circumference. This part of the valve consists of 3 scalloped areas (see diagram 2).

Diagram 2: Normal mitral valve anatomy. (7)



Taken from: Looney Y, Quinton P. Mitral Valve Surgery. Continuing Education in Anaesthesia, Critical Care and Pain. Volume 5, Number 6 2005.(7)

The normal mitral valve area is 4-6cm².

Patients with asymptomatic mitral regurgitation are at risk of sudden death. The risk has been quoted at 1.8% per year. (7)

Incidence and Causes.

Mitral regurgitation can be as a result of a number of different pathologies.

It can develop either acutely or chronically. (5)

Mitral regurgitation can result from abnormalities of: (4)

- Mitral valve leaflets
- Chordae tendinae
- Papillary muscles

It can also be as a result of left ventricular dysfunction. (4) Left ventricular hypertrophy and dilatation can lead to dilatation of the mitral valve orifice. (1) Most cases (up to 50%) are due to rheumatic fever. It is almost always associated with mitral stenosis. (2)

MR can be classified as either primary or secondary or acute or chronic.

Primary causes include: (3,5,7) myxomatous degeneration of the mitral valve, Rheumatic disease, Infective endocarditis (producing rupture of the chordate tendinae), Mitral valve prolapse, and chest trauma.

Secondary causes include: (3,7) Myocardial ischaemia (affecting the papillary muscles/left ventricle causing rupture of the papillary muscles), and dilated cardiomyopathy (producing dilatation of the mitral valve annulus).

Of the above causes of MR, acute (and severe) MR is most commonly due to ruptured chordae tendinae, ruptured papillary muscle, infective endocarditis or chest trauma.

Chronic (slowly progressive) MR is most commonly the result of rheumatic fever.

It commonly coexists with mitral stenosis. Other chronic cause include, congenital/developmental abnormalities of the mitral valve and dilatation/destruction or calcification of the mitral valve annulus.(5)

Physiology and Pathophysiology.

The principal pathophysiological changes with mitral regurgitation are left atrial and ventricular volume overload, reduced forward stroke volume and backward flow of blood into the left atrium. (1,5) Mitral regurgitation leads to a decrease in the left ventricular forward stroke volume. Part of this stroke volume is regurgitated or ejected across the incompetent mitral valve into the left atrium. Mitral regurgitation therefore impacts on the left ventricle, left atrium and ultimately the right ventricle. (8)

Mitral regurgitation typically proceeds in three phases as discussed below.

Acute mitral regurgitation:

The left atrium and ventricle are suddenly exposed to a volume overload. Left ventricular overload occurs secondary to the fact that the left ventricle is now required to pump to two stroke volumes i.e. the forward stroke volume into the aortic root and, the regurgitant volume into the left atrium. Combined, these stroke volumes are referred to as the total stroke volume. This produces an increase in the left ventricular preload (which assists the ventricle in increasing the total stroke volume). Since the ventricle has not had a chance to compensate with hypertrophy, the forward stroke volume and the cardiac output in acute MR are significantly reduced. Likewise, the left atrium has not had sufficient time to compensate for the increased volume and pulmonary congestion quickly develops. (3)

This condition is often a surgical emergency.

Chronic compensated (asymptomatic) mitral regurgitation:

If the left atrium and ventricle have had adequate time to compensate for the volume overload of mitral regurgitation then the ventricle dilates (increases the left ventricular end-diastolic volume) and undergoes eccentric hypertrophy. The left atrium also becomes more compliant. The ventricle dilates and increases the end-diastolic volume (LVEDV). This increase in LVEDV (preload)

assists the ventricle in maintaining a near normal forward cardiac output (although the stroke fraction may be decreased). The compensatory left ventricular (and left atrial) dilatation allows for accommodation of the regurgitant blood volume at much reduced filling pressures. (3, 5) This helps to alleviate the symptoms of pulmonary oedema/congestion. In the chronic compensated phase, patients may remain totally asymptomatic at rest and often with exertion.

Chronic decompensated mitral regurgitation:

The compensated phase can last for many years but the chronic volume overload eventually results in dysfunction of the left ventricle. Progressive myocardial contractile impairment occurs and this leads to decreased ejection fraction. The LVEDV increases resulting in further increases in the left ventricular dilatation and filling pressures. (3) This combination of events leads to reduction in the forward cardiac output and pulmonary oedema secondary to pulmonary congestion. In patients with more severe mitral regurgitation the volume regurgitated into the left atrium may actually exceed the forward stroke volume ejected into the aortic root.

Clinical manifestations and Symptoms.

Patients with chronic mild to moderate mitral regurgitation may be asymptomatic for several years with little evidence of haemodynamic instability. (3)

In the chronic compensated phase patients may remain totally asymptomatic at rest and often with exertion. This phase can last for many years but the chronic volume overload eventually results in dysfunction of the left ventricle. (3)

Patients that have symptomatic mitral regurgitation generally have:

- Exertional dyspnoea
- +/- fatigue and weakness
- Orthopnoea
- Paroxysmal nocturnal dyspnoea.
- Overt pulmonary oedema if severe.

Some patients initially present with atrial fibrillation or a murmur on routine examination.

Patients with acute onset of mitral regurgitation usually present with florid congestive cardiac failure. Shock secondary to decreased cardiac output (cardiogenic shock) is often as a result of a rupture of either a papillary muscle or chordae tendinae.

Diagnosis.

Diagnosis of patients with mitral regurgitation is based on assessment of history examination, CXR and ECG findings.

Physical signs

Auscultation: Forceful or displaced apex beat. (4) Holosystolic (pansystolic) murmur best heard at the apex of the heart that radiates to the axilla. (1) Soft 1st heart sound. Atrial fibrillation Due to compensatory left ventricular hypertrophy and enlargement of the ventricle, the apex beat is displaced and more forceful.

Investigations

ECG findings: The ECG may show non-specific changes. If the patient is in sinus rhythm, P mitrale due to left atrial enlargement may be seen (biphasic P-wave). Atrial fibrillation is commonly seen.

CXR findings: May demonstrate cardiomegaly, especially an enlarged left atrium. (4) This may cause a widening of the carinal angle (splayed carina). Straightened left heart border. Pulmonary congestion/oedema may be present.

Echocardiography can be used to assess the degree of mitral regurgitation and left ventricular function. Colour flow doppler demonstrates the regurgitant jet of blood entering the left atrium. Transoesophageal echocardiography (TOE) is particularly useful as the mitral valve is in close approximation to the oesophagus. (4)

Anaesthetic Implications / Treatment.

Because regurgitant lesions can progress insidiously, left ventricular damage may occur before the patient becomes symptomatic. (1)

Medical treatment has a very limited role if the mitral regurgitation is acute in onset. Sodium nitroprusside is often used to decrease the systemic vascular resistance immediately pre-operatively. This increases the forward stroke volume, decreases the regurgitant volume and reduces pulmonary congestion. (3)

If the patient is also hypotensive, intravenous inotropic agents are also co-administered.

An intra-aortic balloon pump (IABP) can be used to support the cardiac output (improves the myocardial oxygen balance) and stabilize the patient while waiting for urgent surgery.

In patients with chronic MR:

No long-term studies have been conducted looking at the use of peripheral vasodilators.

If the patient is not hypertensive (asymptomatic with good left ventricular function), there is no indication for using vasodilating drugs or angiotensin converting enzyme inhibiting drugs (ACEi).

(3,8) If the patient has left ventricular dysfunction, ACEi drugs and/or beta-blocking agents have been shown to be of benefit. (3,8) Atrial fibrillation is common. Up to 50-75% of patients with mitral regurgitation have atrial fibrillation. Patients may require rate and or rhythm control and systemic thrombo-embolism prophylaxis.

Acute mitral regurgitation warrants urgent mitral valve repair or replacement as the sudden volume overload of the left atrium and ventricle are often not well tolerated. In patients with

mitral regurgitation who develop symptoms but have good left ventricular function, elective surgery should be considered. (3)

Surgical treatment is recommended when the ejection fraction is less than 0.6 and improves survival. (1,9)

Three different operations are used to correct mitral regurgitation: (3,7) MV repair, MV replacement (with preservation of all or part of the mitral apparatus) and MV replacement (with removal of the mitral apparatus). (3)

The general indications for surgery are: (3)

- Patients with symptomatic acute severe MR
- Symptomatic chronic severe MR (even in the absence of left ventricular dysfunction).
- Asymptomatic patients with chronic severe MR and left ventricular dysfunction.

Anaesthesia.

Basic management for patients with mitral regurgitation that need non-cardiac surgery is aimed at avoiding events that are likely to decrease the cardiac output. (1,7)

Prophylactic antibiotics should be administered to prevent endocarditis in patients undergoing surgery or dental procedures. (1)

The haemodynamic aims are to maintain a normal to slightly increased heart rate. The forward stroke volume from the left ventricle is heart rate dependent (but also increases the regurgitant volume). (4) Bradycardia (increased systolic time) should ideally be avoided as this can result in sudden left ventricular volume overload.

If sinus rhythm deteriorates into atrial fibrillation (with a rapid ventricular rate), this will decrease the cardiac output.

Preload should be adequate. Keeping the patient well filled will further facilitate the forward stroke volume. However overfilling may precipitate pulmonary oedema.

Normal to slightly lower systemic vascular resistance (SVR) is required. Sudden increases in SVR are not usually well tolerated and may precipitate sudden left ventricular decompensation. (1) Increased SVR will increase the regurgitant volume.

If the systemic blood pressure falls intraoperatively, this should ideally be managed with further intravenous fluid and increasing the heart rate if the patient is bradycardic. (4)

Sodium nitroprusside (SNP) has been used to reduce the SVR intraoperatively.

Avoid vasoconstrictors if possible. Myocardial contractility should be maintained. Drug induced decreases in myocardial contractility are undesirable as this can worsen any left ventricular dysfunction.

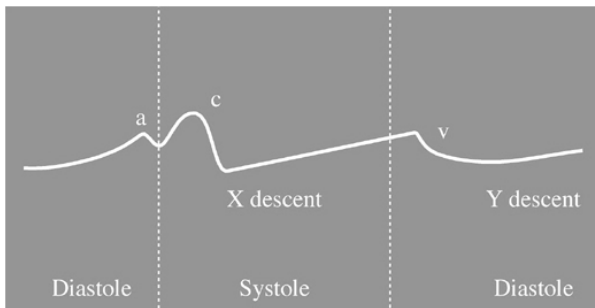
Avoid pulmonary hypertension i.e. avoid hypercarbia, acidosis and hypoxia. Nitrous oxide can be used, but should be used with caution as it can produce pulmonary hypertension.

If surgery is minor and the patient has asymptomatic mitral regurgitation, full invasive monitoring (arterial, central venous, pulmonary artery) is most likely not required. (1)

For major surgery or if the patient is symptomatic or has severe mitral regurgitation invasive haemodynamic monitoring is desirable as it will guide intravenous fluid administration and provide information about cardiac output and onset of decreased myocardial contractility. Pulmonary catheterization (Swan-Ganz floatation catheter) can guide the use of vasodilating

drugs used to decrease the SVR. As blood is regurgitated into the left atrium, large V waves are usually seen on the pulmonary occlusion pressure trace (wedge pressure – see diagram 3 – normal venous waveform).

Diagram 3: Normal central venous waveform. a = atrial contraction, c = bulging of tricuspid valve into right atrium, x = atrial relaxation, v = rise in atrial pressure just before tricuspid opening, y = atrial emptying. (2,10).

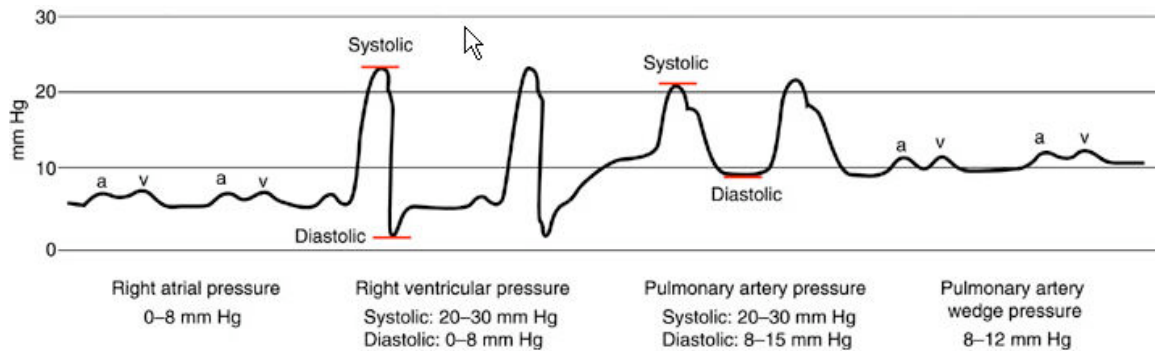


Taken from: www.hku.hk/anaesthe/LearNet/interpretation.htm

Pulmonary capillary wedge pressure (or occlusion pressure) represents the left atrial pressure and estimates the left ventricular end-diastolic pressure (see diagram 4).

With mitral regurgitation, large v waves and a rapid y descent are typically seen on the pulmonary artery waveform. (5) The size of the v wave correlates well with the magnitude of the regurgitant flow of mitral regurgitation. (1)

Diagram 4: Pressure tracing during the insertion of a pulmonary artery catheter.(11)



Taken from: <http://connection.lww.com/Products/morton/documents/images/Ch17/jpg/Ch17-058.jpg>

Provided SVR and bradycardia do not fall significantly, spinal and epidural anaesthesia are generally well tolerated. (5)

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PREVENTION OF INFECTIVE ENDOCARDITIS.

(Based on the most recent AHA guidelines 2007)

Introduction.

Infective endocarditis is an uncommon but life-threatening infection. Patients still have a high morbidity and mortality rates in spite of advances in diagnosis, antimicrobial therapy and surgical techniques.

Infective endocarditis is thought to result after the formation of nonbacterial thrombotic endocarditis on the surface of a cardiac valve where there has been endothelial damage followed by bacteraemia, adherence of the bacteria to the thrombotic endocarditis and proliferation of bacteria within the vegetation.

The nonbacterial thrombotic endocarditis occurs where there is turbulent flow, such as produced by certain types of congenital and acquired valvular lesions. Platelets and fibrin deposit on the surface of damaged endothelium, which has resulted from the turbulent flow.

Transient bacteraemia occurs whenever there is trauma to a mucosal surface that is populated by endogenous microflora, particularly the gingiva, oropharynx, gastrointestinal tract, and genitourinary tract. The ability of the microbial species to adhere to specific sites determines the site of infection. In the animal model, bacterial surface components in streptococci, staphylococci and enterococci function as adhesins, allowing them to attach to cardiac valves. When the microbes adhere to the vegetation on the valve, further deposition of fibrin and platelets occurs. Eventually, more than 90% of the microorganisms in mature vegetations are no longer in the active growth phase and are therefore less responsive to the bactericidal effects of antibiotics.

The viridans group of streptococci are part of normal flora on the skin, oral, respiratory and gastrointestinal mucosa and they cause at least 50% of the cases of community acquired native valve infective endocarditis.

The rationale for the use of prophylactic antibiotics to prevent infective endocarditis is based on the following factors:

1. Bacteraemia causes endocarditis.
2. Viridans group streptococci are part of the normal oral flora and enterococci are part of the normal gastrointestinal and genitourinary tract flora.
3. These micro organisms are usually susceptible to antibiotics.
4. Antibiotic prophylaxis prevents the development of experimental endocarditis in animals.
5. There have been a large number of documented (albeit poorly documented) case reports of infective endocarditis after dental procedures.
6. There is an awareness that bacteraemia caused by viridans group streptococci is associated with dental procedures.
7. The risk of significant adverse reactions to an antibiotic is low in an individual patient.
8. Morbidity and mortality from infective endocarditis is high.

Oral/Dental procedures.

However there is still a lack of published data that demonstrates a benefit from prophylaxis. Cases of infective endocarditis caused by oral bacteria probably result from the low exposures to bacteraemia that result from routine daily activities such as chewing, brushing and flossing teeth and not from a dental procedure. The vast majority of patients who develop infective endocarditis have not had a dental procedure within 2 weeks.

The ability of antibiotic therapy to prevent or reduce the bacteraemia associated with dental procedures is controversial. Clinical studies on the efficacy of antibiotic prophylaxis to prevent infective endocarditis in susceptible patients are retrospective, non-randomised and not placebo controlled. Some suggest that there is a benefit from prophylaxis but a study from the Netherlands concluded that dental or other procedures caused only a small fraction of cases of endocarditis and that prophylaxis would prevent only a small number of cases even if it were 100% effective. The same authors found that among the patients in their study, five out of twenty cases of endocarditis occurred despite prophylaxis. The AHA states that the presence of dental disease may increase the risk of bacteraemia and that there should be a shift in emphasis away from dental procedures and antibiotic prophylaxis toward a greater emphasis on improved access to dental care and oral health in patients with underlying cardiac conditions that predispose to infective endocarditis.

The underlying conditions that have the highest predisposition to the acquisition of endocarditis over a patient's lifetime are rheumatic heart disease, mitral valve prolapse (particularly when associated with mitral regurgitation), cardiac valve replacement (higher still for those with previous endocarditis), and infective endocarditis and congenital heart disease. Infective endocarditis has a worse outcome if it occurs on a prosthetic valve rather than a native valve. The mortality is 20% if viridans group streptococcal endocarditis occurs on a prosthetic valve and 5 % if it occurs on a native valve. Patients with relapsing or recurrent infective endocarditis are at greater risk of heart failure and need for replacement valves. There are also at greater risk of future episodes of endocarditis. Patients with complex congenital cyanotic heart disease and those with postoperative palliative shunts or conduits, or other prostheses have a high lifetime risk of endocarditis. Patients within six months of repair of congenital heart disease have not had a chance for the prosthetic material to become reepithelialized are at risk for infective endocarditis.

The AHA recommends prophylaxis with dental procedures for the following cardiac conditions:

1. Prosthetic cardiac valve
2. Previous infective endocarditis
3. Congenital heart disease only when there is:
 - a. Un-repaired cyanotic congenital heart disease (including those with palliative shunts and conduits)
 - b. Completely repaired congenital heart disease with prosthetic material or device during the first six months after the procedure
 - c. Repaired congenital heart disease with residual defects at or adjacent to the site of a prosthetic patch or device (which inhibits endothelialization)
4. Cardiac transplant patients who develop a valvular heart disease.

The AHA no longer recommends prophylaxis for the patients with mitral valve prolapse because although it is the most common underlying condition that predisposes to infective endocarditis in the western world, the absolute incidence of endocarditis is extremely low for the entire population with mitral valve prolapse.

Many fewer patients would be candidates to receive prophylaxis under these new guidelines. The administration of prophylactic antibiotics is not without risk, however, and the widespread use of antibiotics promotes the emergence of resistant bacteria.

In the setting of a dental procedure, the AHA states that a single dose of amoxicillin or ampicillin is safe and the preferred prophylactic agent for those with no hypersensitivity to penicillin. The dose should be administered in a single dose before the procedure, but if it is omitted, it can be given for up to two hours after the procedure. If the patient were febrile before the procedure, it would be prudent to investigate for the presence of coincidental endocarditis. Prophylaxis is recommended for any dental procedure that involves the gingival tissue or periapical part of the tooth and when the oral mucosa is perforated in the patients with the above risk factors. It is not recommended for the injection of local anaesthetic through non-infected tissue or for trauma to the lips and oral mucosa in the context of a dental procedure.

Amoxicillin is the preferred choice for oral therapy, as it is well absorbed. For those allergic to penicillin, cephalexin (or another first-generation cephalosporin), clindamycin, azithromycin or clarithromycin is recommended.

Respiratory tract procedures.

Respiratory tract procedures can cause transient bacteraemia and prophylaxis can be considered in the patients with the aforementioned conditions who are undergoing an invasive procedure of the respiratory mucosa such as tonsillectomy or adenoidectomy. Bronchoscopy is not an indication for prophylaxis unless there will be an incision of the mucosa. The patient undergoing drainage of an abscess or empyema should have a regimen that contains an agent active against viridans group streptococci. If the infection is due to staphylococci, an anti staphylococcal agent is recommended.

Gastrointestinal/Genitourinary procedures.

Enterococci are present in the genitourinary and gastrointestinal tract. Infections at these sites are often polymicrobial, but it is only the enterococci that are likely to cause endocarditis. Prophylaxis is not recommended for those patients who undergo gastrointestinal or genitourinary procedures (including diagnostic gastroscopy and colonoscopy). In those with established infection or those who receive antibiotic therapy to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary procedure, it may be reasonable to include an agent active against enterococci such as ampicillin, penicillin, piperacillin or vancomycin.

Body surface procedures.

Skin or musculoskeletal infections are often polymicrobial, but only the staphylococci and beta-haemolytic streptococci are likely to cause infective endocarditis. If the patient with one of the above conditions were to undergo a procedure that involves infected skin or musculoskeletal

tissue, the therapeutic regimen should contain an agent active against staphylococci and beta-haemolytic streptococci such as an anti-staphylococcal penicillin or cephalosporin.

The patient who is already receiving long-term antibiotic therapy who is at risk should receive another antibiotic from a different class. These patients have viridans group streptococci that are relatively resistant to penicillin or ampicillin and should receive, clindamycin, azithromycin or clarithromycin for dental procedures. If possible, it would be preferable to delay a procedure for ten days after completion of antibiotic therapy.

Cardiac surgery.

Patients who are about to undergo cardiac surgery should have a preoperative dental examination so as to decrease the likelihood of late prosthetic cardiac valve endocarditis. The patients who are undergoing cardiac surgery for placement of a prosthetic valve or other prosthetic intracardiac or intravascular material should receive perioperative prophylactic antibiotics. Prophylaxis should be directed against staphylococci and be of short duration. A first generation cephalosporin is appropriate unless there is a high prevalence of methicillin resistant staphylococcus aureus, when vancomycin may be used. The antibiotics should be administered immediately before the procedure, repeated during long operations and used for no more than 48 hours postoperatively.

ANTIBIOTICS FOR SURGICAL PROPHYLAXIS.

Wound infections are the most common hospital-acquired infections in surgical patients. Appropriate antibiotic prophylaxis can reduce the risk of postoperative wound infections. Inappropriate use of antibiotics can favour the emergence of antimicrobial resistance and it has been shown that 30-90% of surgical antibiotic prophylaxis is inappropriate. Most commonly, the duration of therapy is too long or the antibiotic is administered at the inappropriate time.

Antibiotic prophylaxis is appropriate in the case of clean-contaminated or contaminated surgery or when an artificial device or prosthesis is inserted. Clean-contaminated surgery is defined as operations when the respiratory, alimentary or genitourinary tract is penetrated under controlled conditions such as in laryngectomy, cholecystectomy, and transurethral resection of the prostate. Contaminated operations are those with macroscopic soiling of the operative field such as in large bowel resection, biliary or genitourinary surgery with infected bile or urine.

Antibiotics should be administered via the parenteral route after the induction of anaesthesia. When vancomycin is used, it is given as an infusion over one hour prior to surgery. Rectal metronidazole should be given 2-4 hours preoperatively and oral tinidazole, 6-12 hours prior to surgery. Usually, only a single dose of antibiotic at the beginning of surgery is sufficient unless the procedure is of greater than three or four hours duration. Some vascular procedures require 48 hours of antibiotics for prophylaxis, and the patient with peritonitis or faecal soiling of the peritoneum should undergo a full course of antibiotics. The antibiotic should be chosen on the basis of the most likely pathogen and with the narrowest antibacterial spectrum. Most infection is caused by the patient's own organisms and in those who have been in hospital for a long period of time, this flora may include multi-resistant organisms. Prophylaxis does not need to cover all bacterial species, just those most likely to cause infection. It is important to avoid the use of broad-spectrum antibiotics, particularly those that may need to be used to treat serious sepsis such as the third generation cephalosporins.

The commonly used antibiotics for surgical prophylaxis include:

- Intravenous first generation cephalosporins: cephazolin or cephalothin
- Intravenous gentamicin
- Intravenous or rectal metronidazole when anaerobic infection is likely
- Oral tinidazole to prevent anaerobic infection
- Intravenous flucloxacillin for sensitive staphylococci
- Intravenous vancomycin for methicillin resistant staphylococcus aureus (MRSA)

Routine use of vancomycin should be avoided to avoid the emergence of vancomycin resistant organisms. It should be used to replace cephalosporin or penicillin if the patient is known to be infected or colonised with MRSA, if there is a high risk for MRSA colonization and the patient is having major surgery, the patients having re-operations for prosthetic cardiac valve, joint or vascular surgery or the patient is hypersensitive to penicillin and cephalosporins.

Antibiotics cannot be relied on to compensate for poor surgical technique or inadequate medical management (eg of diabetes).

If the patient has a history of allergy to beta-lactams, they should be avoided. A history of anaphylaxis, urticaria or angioedema with penicillin is a contraindication to cephalosporin use due to cross reactivity.

The recommendations for antibiotics for various types of surgery are presented below. For the patient undergoing abdominal surgery, meta-analysis of trials has shown that prophylaxis is appropriate. The anaerobic cover can be omitted in the patients at low risk such as upper gastrointestinal surgery in those with normal gastric function, no obstruction or bleeding and no malignancy; and the patients having biliary surgery who are not diabetic, under 60 years of age, having elective cholecystectomy with a low risk of bile duct exploration. There is no evidence to support the use of antibiotics for routine upper and lower gastrointestinal endoscopy except for those having oesophageal dilatation or endoscopic retrograde cholangiopancreatography.

The patients undergoing hernia repair do not require prophylaxis unless prosthetic material is being used, in which case cephalothin or cephazolin are indicated.

Patients who are having urological surgery with significant bacteriuria should be treated preoperatively to prevent postoperative sepsis.

Antibiotics are not recommended for the vascular surgical patients having carotid, brachia or varicose vein surgery. For those having arterial reconstruction of the lower limb or aorta, there is some evidence that a longer duration of up to 48 hours of antibiotics may be required.

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Type of surgery	Commonest pathogens	Antibiotic choice
Abdominal surgery	Gram negative bacilli (E.coli, Klebsiella)	Cephalothin or cephazolin, or gentamicin
	Anaerobic Gram-negatives (Bacteroides)	Metronidazole
Cardiac surgery	Staphylococci	Cephalothin or cephazolin OR the combination of flucloxacillin and gentamicin
	Aerobic Gram negatives	(Vancomycin and gentamicin for repeat surgery)
Head, neck and thoracic surgery	Aerobic and microaerophilic streptococci, anaerobes	Cephalothin or cephazolin
Hysterectomy	Anaerobes, Gram negative bacteria	Cephalothin or cephazolin PLUS tinidazole or metronidazole
Caesarean section	Gram negative bacilli, streptococci, anaerobes	Cephalothin or cephazolin
Orthopaedic surgery	Staphylococcus aureus, (less commonly, aerobic Gram-negative bacilli and anaerobes)	Cephalothin or cephazolin or flucloxacillin (Vancomycin for repeat joint replacements)
Urological surgery	Gram negative enteric bacteria, enterococci	Gentamicin
Vascular surgery	Staphylococci, Gram negative bacteria, anaerobes	Cephalothin or cephazolin OR the combination of flucloxacillin and gentamicin (When vancomycin is indicated, use with gentamicin)
Lower limb amputation	Clostridium	Benzyl penicillin or metronidazole
Neurosurgery	Staphylococci, diphtheroids	Cephalothin or cephazolin or flucloxacillin

THE BASICS OF PAIN

Introduction.

The International Association for Study of Pain (IASP) defines pain as “an unpleasant sensory **and emotional** experience associated with actual or potential tissue damage or described in terms of such damage (1).

It is to be noted that pain is not just a physical sensation, but also an **emotional experience**. There may be a strong emotional component contributing to the pain experience. A simple definition of pain is “*Pain is what the patient says, hurts (2)*” The emphasis is on *the patient’s* experience.

The emotional component is variable from person to person and in the same person from time to time. Management of pain has to take this fact into consideration. The patient must be believed about the pain.

The untreated or the under-treated pain condition can cause physical damage and also worsen the pain experience by muscle spasm, peripheral and central sensitization and recruitment and by muscle spasm. Unrelieved acute pain can cause chronic pain, and long standing pain can cause anatomical changes in the nervous system.

Pain can be classified in several ways, but the most relevant, in terms of therapeutic options, is the classification of pain into nociceptive and neuropathic pain.

Apart from the identification of the type of pain, it is also necessary to quantitate pain. Several scoring systems are available like the numerical scale, but it needs to be remembered that the patient is the only person who can quantitate his/her pain.

Chronic pain is defined as pain which persists a month beyond the usual course of an acute disease or a reasonable time for an injury to heal, or is associated with a chronic pathological process which causes continuous pain, or pain which recurs at intervals for months or years (3).

Mechanism of pain sensation.

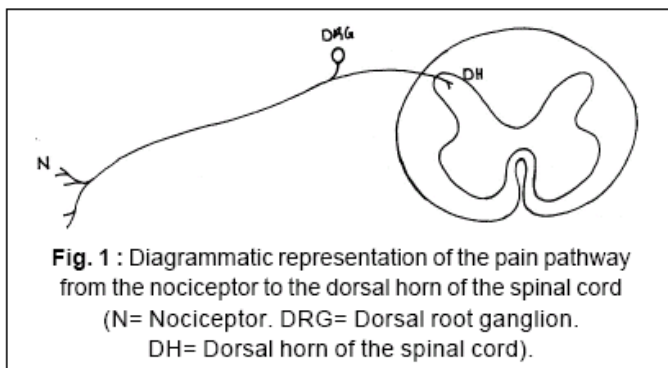


Fig. 1 : Diagrammatic representation of the pain pathway from the nociceptor to the dorsal horn of the spinal cord

Fig. 1 shows an oversimplified pain pathway from the periphery up to the dorsal horn of the spinal cord. The peripheral bare nerve ending subserving pain is called the **nociceptor**. Mechanical, thermal, electrical or chemical stimulation of the nociceptor causes an electrical impulse to be generated and transmitted up the peripheral nerve through A-delta and C fibres to the dorsal horn of the spinal cord. In the dorsal horn cells, the impulses get modified before onward transmission to the thalamus and the cerebral cortex where the pain is appreciated.

Pain must be treated. Why?

1. **Relieving suffering:** First and foremost, pain is suffering and it is a basic human right to expect relief from pain. This applies whether pain is acute or chronic.
2. **Muscle spasm:** Pain causes reflex muscle spasm. This has two negative implications:
 - a). It can cause respiratory embarrassment. Pain in upper abdominal surgery is a classical case in point. Muscle spasm can cause regional hypoventilation and contribute to post-operative respiratory problems. In a multiple rib fracture, pain relief may be the single factor that can avoid the need for artificial ventilation.
 - b). The muscle spasm itself can be a major cause of pain. Even short-term muscle spasm can cause severe pain eg. back spasm – but when long-lasting, it may result in the development of myofascial trigger points. These areas of sustained contraction then act as new foci of pain.
3. **Untreated pain will keep getting worse (4).** This is true for surgical trauma too, but understandably, is even more relevant in chronic pain. There are several neurophysiological reasons for this:
 - a). **Recruitment of nociceptors:** Silent’ or ‘sleepy’ nociceptors are those that do not respond to noxious stimuli normally; but are activated in the inflamed tissues. Once they are recruited, the same degree of peripheral stimulus generates more number of electrical impulses, thereby resulting in worsening of pain.
 - b). **Central recruitment:** With persisting pain, adjacent spinal segments (or adjacent supraspinal areas) get recruited, so that pain gradually spreads to larger areas (5).
 - c). **Sensitisation of nociceptors :** The nociceptors get sensitized with time so that the response threshold is lowered. Chemicals involved in the inflammatory process mediate this peripheral sensitization. Other agents also implicated are purines, cytomines, leukotrienes, nerve growth factor and various neuro-peptides.
Prostaglandins are believed to have a major role in this process of sensitization and this accounts for the reduction in pain obtained with the use of Non-steroidal anti-inflammatory drugs (NSAIDs) (6).
 - d). **Central sensitization (“wind-up” phenomenon”):**
The dorsal horn cells get sensitized. This is compared to a wound-up spring, hence the common term, “wind-up” phenomenon (7). When the painful stimulus persists, the same peripheral input produces progressively increasing electrical response from the dorsal horn cell. It manifests as:
 - an increase in the receptive field for sensitised dorsal horn neurons
 - an increase in the duration of response and
 - a reduction in the response threshold.

N-Methyl D Aspartate (NMDA) is believed to be the most important neurotransmitter involved in the “wind-up” mechanism (8).

4. **Neuroanatomical re-organisation:** This often seems to accompany central sensitization. In the face of continued barrage of pain impulses, the integrity of the dorsal horn of the spinal cord gets disturbed so that neurons subserving input from A-beta fibres form functional connections with neurons in lamina-2 subserving input from A-delta and C fibres. Thus, stimulation of A-beta fibres, which normally causes sensations only of touch and pressure, in this case causes pain (8). This is called **allodynia** (such abnormal sensations can occur also in peripheral nerve lesions).
5. **Anatomical and genetic changes:** It has been clearly proved now that persistent unrelieved pain can cause anatomical changes in the nervous system, as well as genetic changes in the dorsal horn cell (9).

Points of Clinical Application

1. *Pain must be treated early. Unrelieved pain causes worsens pain both in extent and severity.*
2. *In long-standing pain associated with central sensitization, NMDA antagonism with ketamine would have a role to play.*
3. *Once anatomical changes in the nervous system have occurred in chronic pain, total relief may be unlikely.*

Classification of Pain.

The peripheral nerve ending (nociceptor) transmits the pain impulse to the dorsal horn of the spinal cord, where it gets modified before onward transmission to the brain. Any pain caused primarily by stimulation of the nociceptor can be said to be **nociceptive** pain. If pain is **not** caused by a stimulus applied to the nociceptor, but is caused by impulse generation within the pathway proximal to the nociceptor (this could be in the nerve, the spinal cord or the brain), it is called **neuropathic** pain (fig 2).

This does not mean that all nociceptive pains are similar in presentation or management. For example pain arising out of smooth muscle spasm can be very different from the pain of skeletal muscle spasm.

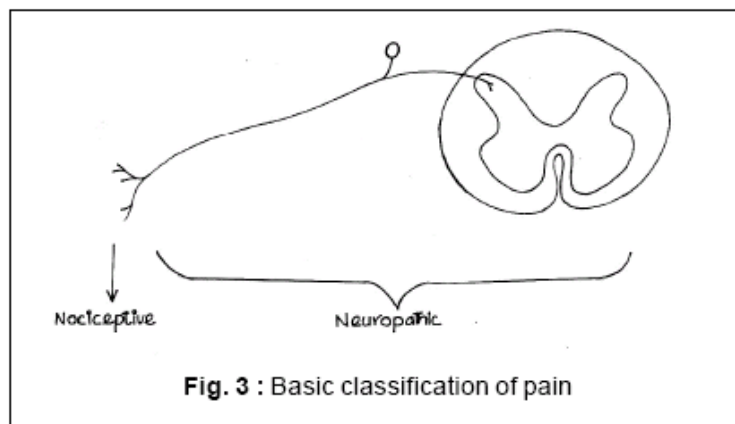


Fig. 3 : Basic classification of pain

Fig. 2: Basic classification of pain

Nociceptive pain can be subdivided to somatic and visceral pain, depending on site of origin.

Neuropathic pain can be of three sub-types:

- i) Neural injury pain
- ii) Nerve compression pain and
- iii) Complex Regional Pain Syndrome (CRPS).

Neural injury pain can be said to involve anatomical abnormality in peripheral nerves, in pain receptors or in the central pain pathway. The following three features help to diagnosis a neuropathic pain.

- a). The nature of the pain may be shooting, stabbing, pricking, aching or burning.
- b). It has a neural or dermatomal distribution.
- c). It is often associated with abnormal sensation in the area of pain. This can take the form of hypoaesthesia or hyperesthesia. Unfortunately it often takes the form of *dysaesthesia*, that is, an unpleasant abnormal sensation. Allodynia and hyperalgesia are examples. Hyperalgesia is increased response to a stimulus, particularly a repetitive stimulus, as well as an increased threshold (an exaggerated response with an increase in pain threshold).

Nerve compression pain occurs when there is extrinsic pressure on the neural structure, eg. a nerve root compression in prolapsed inter-vertebral disc or with collapsed vertebrae from metastatic lesions.

Neuropathic pain can also be sub-classified into peripheral and central, depending on site of origin of abnormal impulse. The relevance is that central neuropathic pains often behave differently from peripheral neuropathic pains, particularly in their response to drugs. Central neuropathic pains are the commonest in injury to the central nervous system – eg. Spinal cord injuries, stroke etc (10).

It must be remembered that pain originally of peripheral nerve origin, can become centrally established – by somehow altering the CNS. Once this has happened, a peripheral nerve block or neurolysis may not successfully remove the pain.

Points of clinical application

1. *Depending on site of origin of pain, different types of pain may warrant different modalities of management. It is necessary to understand the type of pain, to decide on management.*
 2. *Neuropathic pain is often burning, aching, stabbing or pricking, is of neural or dermatomal distribution and is usually associated with abnormal sensation in the area of pain*
-

Evaluation of pain:

A proper evaluation of pain is essential for proper treatment. Patients often have more than one type of pain. Some of them may be unrelated to, or only indirectly related to the basic disease. The different pains eg. muscular, neuropathic etc. would need different modalities of treatment.

Tools for Evaluation of Pain

To assess the severity of pain and the success of treatment, some form of quantitation of pain is necessary. Many pain scoring systems are available.

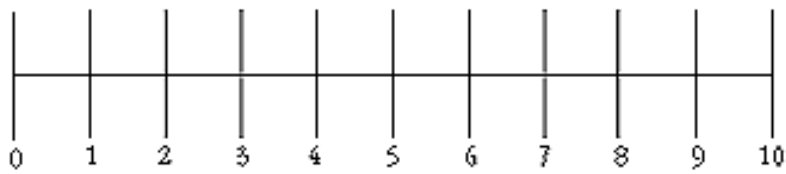
- a) **Categorical:** A four or five point scale grading the pain as none, mild, moderate, severe and excruciating etc. This scale lacks sensitivity, but it has the advantage of simplicity.
- b) **Numerical scale:** This is an 11 point scale where “0” means no pain and “10” is the worst imaginable pain.
- c) **Visual Analogue Scale (VAS):** A 100 mm scale with no pain at one end and worst imaginable pain at the other, is commonly used. There are no graduations on the side that the patient sees; the 100 graduations are only visible to the person who makes a record of the patient’s evaluation (11).
- d) **McGill Pain Questionnaire (MPQ):** MPQ measures the sensory, affective, evaluative and other miscellaneous aspects of pain, thus measuring pain multi-dimensionally. The questionnaire contains about 20 aspects. 1 to 10 represents sensory aspects of pain, 11 to 15 represent affective aspect of pain, 16 represents evaluative aspect of pain, 17 to 20 other miscellaneous aspects of pain. Each subunit has 2 to 5 words under them, representing increasing degree of pain and numerical value. The sum of all points gives a rank value, which is termed the Pain Rating Index (12).
- e) **Happy-sad face** – A child or an illiterate person could use a set of faces to indicate the severity of his pain. This scale shows a child’s face in different moods, the child is asked to select the facial expression that best suites the pain expression. This assesses the affective and fear component of pain.

Evaluation of outcome in chronic pain

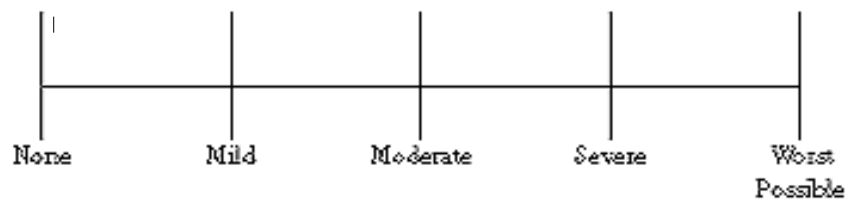
Most patients with chronic pain get some degree of response to any new modality of treatment that is introduced. This could be partly due to placebo effect and partly due to reduction of the emotional element of pain. So it is to be remembered that success of a treatment regime can be decided on only if the positive response lasts long enough – at least for three weeks. And the evaluation is best made in terms of quality of life too, not just with a pain score.

Template 2. Pain Intensity scales

Numeric



Categorical



Visual Analogue Scale



Pain Relief Scale



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MANAGEMENT OF POSTOPERATIVE PAIN

Introduction.

Pain, a common presenting feature of many disease processes, is usually associated with actual or impending tissue damage. Acute pain in the perioperative setting is defined as pain that is present in a surgical patient because of pre-existing disease, surgical procedure or a combination of these. It is an unpleasant and inevitable component of the post surgical experience. Any individual, who undergoes surgery, has the right to expect and obtain adequate relief of postoperative pain. Patients, however, continue to silently suffer postoperative pain because of lack of a concerted effort on the part of the anaesthetic and surgical team to relieve this pain. If one considers adequate pain relief to be a basic human right of the patient, failure to relieve pain is tantamount to a moral and ethical lapse on the part of the doctor.

The modern anaesthetist must see oneself as a perioperative physician and take on the responsibility to ensure patient comfort throughout the pre-operative, intra-operative and post operative periods. Though most of us administer generous doses of potent analgesics to patients during surgery with the objective of providing good intra-operative analgesia, the same quality of care often does not permeate into the postoperative period. The end result is a dissatisfied, miserable and anxious patient. Besides the distress patients are often unable to breathe adequately, cough effectively, move enough to tend to their own daily needs or participate in their own rehabilitation. This often results in feelings of helplessness, fear, anxiety and depression. Thus, there is a definite need for doctors involved in the postoperative care of a patient to not only understand the adverse effects of pain, but also to provide a comprehensive and effective pain management plan to their post surgical patients.

Adverse effects of perioperative pain (1, 2 ,3).

Pain results in physiological and psychological responses in the patient, the majority of which are detrimental to postoperative outcome. It therefore stands to reason that adequate relief of pain might translate to better perioperative outcome.

Physiologic responses.

Severe acute pain produces an increase in sympathetic tone that manifests as an increase in heart rate, blood pressure, cardiac output, and systemic and coronary vascular resistances. These adverse cardiovascular effects can be minimised by epidural anaesthesia that is high enough to block the cardiac sympathetic fibres (T1 to T5). Effective perioperative analgesia by other means also affords cardiovascular protection. Pain associated with thoracic and upper abdominal surgery can cause significant postoperative respiratory dysfunction. Pain causes an increase in muscle tone around the site of injury. This “muscle splinting”, coupled with voluntary reductions in respiratory muscle excursions, causes reduction in lung volumes (tidal volume, vital capacity and functional residual capacity), regional lung collapse (atelectasis) and reduced alveolar ventilation, all of

which ultimately result in hypoxaemia and hypercapnia. These respiratory changes also result in a reduced ability to cough, retention of secretions and increased risk of chest infections. Adequate perioperative pain relief, coupled with breathing exercises, can reverse these adverse respiratory effects.

Increased sympathetic activity associated with pain also results in decreased gastrointestinal motility (gastric stasis and paralytic ileus), increased intestinal secretions and increased smooth muscle sphincter tone. Continuation of epidural anaesthesia with local anaesthetics for several days into the postoperative period helps not only to improve gastrointestinal motility through direct effect of the epidural blockade, but also minimises the need for opioids (and its associated adverse effects on gastrointestinal motility).

The neuroendocrine and metabolic changes that constitute the stress response to surgery result in an aggravated catabolic state that results in weight loss and negative nitrogen balance. Maintenance of epidural anaesthesia with local anaesthetics for 48 to 72 hours into the postoperative period has a salutary effect on these adverse metabolic effects.

Psychological responses.

Acute postoperative pain causes fear and anxiety in hospitalised patients. If left unattended, it can progress to anger, resentment and animosity towards medical personnel who may be perceived as withholding pain relief. Sleep deprivation may aggravate these feelings. Adequate attention to pain relief can help in promoting a feeling of well being which has a positive influence on postoperative outcome.

Clinical assessment of acute pain

Pain can be evaluated by various scoring systems. Irrespective of the scoring system used, one must record postoperative pain both at rest and during specifically directed movement (chest physiotherapy for thoracotomies, passive knee movements following knee surgery, etc). It should be recorded as frequently as once in 5 minutes during the initial phase when bolus injections of intravenous opioids or epidural opioids / local anaesthetics are being given in an incremental manner. Once adequate basal analgesia has been established, the frequency of assessment can be reduced to once every 2 hours during the first 24 to 48 hours, and once every 4 hours thereafter. In addition, pain scores should be considered along with sedation scores and the traditional ward recordings of temperature, pulse rate, blood pressure and respiratory rate. These six observations constitute the minimum set of data to be recorded in the postoperative chart (with pain score and sedation score being given the status of the 5th and 6th vital signs). Recording postoperative pain is one way of focusing the attention of all caregivers to the presence of acute postoperative pain, and the consequent need for its management.

Management of acute postoperative pain.

Management strategies for postoperative pain are aimed at reducing a patient's pain to a tolerable level. Complete abolition of pain should not be the objective and is certainly not desirable. Though the traditional approach has been to begin pain therapy when surgery is complete, the concept of "preemptive analgesia" has become increasingly popular wherein antinociceptive treatment is started before the onset of pain. Such treatment prevents the establishment of altered central processing that normally amplifies postoperative pain by sensitising the central nervous system to sensory input. Just as "balanced anaesthetic techniques" are used to meet the intraoperative anaesthetic needs of patients by making use of several agents, "balanced analgesia" uses several modalities of pain management to provide a pain- and stress-free state, thereby promoting good postoperative outcome. Multimodal technique of pain management involves administration of two or more drugs that act by different mechanisms via a single route (eg. epidural opioids + local anaesthetics +/- clonidine) for providing superior analgesic efficacy with equivalent or reduced adverse effects. As recommended by the American Society of Anesthesiologists (ASA), whenever possible, anaesthetists should employ multimodal pain management therapy.

Systemic opioids (4).

Systemic opioids have been the mainstay of pain management in the past and still continue to be a popular technique around which other strategies are built. All opioids given in equianalgesic doses produce the same analgesic effect. Opioids are usually administered by oral, rectal, intramuscular (IM), intravenous (IV), subcutaneous (SC) or transdermal routes. Ideally, opioid administration should begin with an individualised prescription tailored to the needs of the patient. The prescription should indicate the agent, dose, frequency and route of administration. Age rather than weight is a better predictor of opioid requirement in the first 24 hours after surgery. The average 24-hour morphine requirements (in mg) using the patient controlled analgesia technique following major surgery in patients aged between 20 and 70 years is given by the formula 100 – age in years. Thus, a 40-year old will need 60 mg of morphine in 24 hours. This simple formula can be used to initiate systemic opioid therapy in the immediate postoperative period.

Specific opioids.

Codeine is classified as a weak opioid, but the molecule itself is devoid of any analgesic activity. Codeine-6-glucuronide is the principle metabolite, but it is also of similar potency to the parent drug. A minor pathway metabolises codeine to morphine (2-10% of dose given) and this accounts for most of the analgesic activity. The enzyme responsible for this minor pathway is cytochrome isoenzyme P450 (CYP) 2D6, which is lacking in 9% of Caucasians.

Codeine is usually combined with paracetamol which helps in providing additional pain relief.

Dextropropoxyphene is also a weak opioid that is often combined with paracetamol for pain relief. However the incidence of dizziness is very high. Nordextropropoxyphene, the major metabolite is excreted renally and its accumulation can result in central nervous system (CNS), respiratory or cardiovascular depression.

Diamorphine (also called diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine. Diamorphine and MAM are far more lipid soluble than morphine and can penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine. There is no difference between parenteral diamorphine and morphine in terms of analgesic and side effects.

Methadone is commonly used for maintenance therapy in patients who are opioid addicts because of good oral bioavailability (60-95%), high potency and longer duration of action. In addition, its lack of active metabolites, low cost, NMDA antagonistic activity and serotonin reuptake inhibitor activity is useful in treating chronic pain. Its use in treating acute pain is limited by long and unpredictable duration of action and risk of accumulation of metabolites.

Morphine is the opioid most widely used in the management of acute pain. It is metabolised into morphine-6-glucuronide and morphine-3-glucuronide in the liver. Morphine-6-glucuronide is a u-opioid receptor agonist and is more potent than morphine while morphine-3-glucuronide has low affinity to opioid receptors and has no analgesic activity. It is sometimes associated with neurotoxic side effects such as allodynia, hyperalgesia and myoclonus. Both the metabolites accumulate in presence of renal dysfunction, at higher doses, older age group and with oral administration.

Oxycodone is a potent oral opioid agent, used in acute pain management for patients able to tolerate oral intake. It is metabolized to noroxycodone and oxymorphone, both of which are weakly active contributing minimally to any clinical effect. It is available in immediate-release and controlled-release formulations and can also be used as “step-down” analgesia following parenteral opioid regimens.

Pethidine is a synthetic opioid still widely used despite its multiple disadvantages. Studies have found that it is no better than morphine in the treatment of renal and biliary colic, including its effects on the sphincter of Oddi. Pethidine induces more nausea and vomiting than morphine when used parenterally. Accumulation of its active metabolite, norpethidine, is associated with neuroexcitatory side effects (tremors, twitches, multifocal myoclonus and seizures). As impaired renal function increases the half-life of norpethidine, patients in renal failure are at increased risk of norpethidine toxicity.

In view of these facts, the use of pethidine should be discouraged in favour of other opioids.

Fentanyl is increasingly used in the treatment of acute pain because of its lack of active metabolites and fast onset of action. But it has the limitation of have a short half-life.

Tramadol is an atypical centrally-acting analgesic because of its combined effects as an opioid agonist (mainly its metabolite, O-desmethyl-tramadol at the u-opioid receptor) and a serotonin and noradrenaline reuptake inhibitor. It is listed as a weak opioid by the World Health Organisation. The risk of respiratory depression is significantly lower at equianalgesic doses and does not depress the hypoxic ventilatory response. It has limited effects on gastrointestinal motor function

with respect to morphine - causing less constipation and lesser effects on gastric emptying/post operative bowel recovery.

Nausea and vomiting are the most common side effects and tramadol does not increase seizure incidence when compared to other analgesic agents.

Routes of systemic opioid administration (4).

Oral Route.

Oral administration is simple, non-invasive, has good efficacy in most settings and high patient acceptability. Other than in the treatment of severe acute pain and providing there are no contraindications to its use, it is the route of choice.

Limitations include nausea/vomiting or delayed gastric emptying, when absorption is likely to be impaired. Rates of absorption will vary according to the formulation of the drugs. Bioavailability will also vary between drugs. Titration of pain relief with oral analgesic drugs is slower compared to other routes.

Rectal Route.

Is useful when other routes are unavailable. It results in uptake into the submucosal venous plexus of the rectum that drains into the inferior, middle and superior rectal veins. Drug absorbed from the lower half of the rectum through the inferior and middle rectal veins will pass into the inferior vena cava, bypassing the portal system. Any absorption into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Limitations to this route include variability of absorption, possible rectal irritation, cultural factors and contraindications such as rectal lesions, recent colorectal surgery and immune suppression.

Intramuscular and Subcutaneous Routes.

IM and subcutaneous (SC) injections of analgesic agents are still commonly employed for the treatment of moderate or severe pain. The quality of pain relief is less with IM or SC regimens than IV dosing. Absorption may be impaired in conditions of poor perfusion (eg. hypovolaemia, shock, hypothermia or immobility) leading to inadequate early analgesia and late absorption of the drug depot when perfusion is restored.

The placement of SC plastic cannulae allow the use of intermittent SC injections without repeated skin punctures and also enables the provision of continuous SC infusions, which are as effective as continuous IV infusions.

Intravenous Route.

Table - 1 : Intravenous dosage of commonly used opioids.

<i>Drug Dosage</i> <i>Intravenous bolus</i>	<i>Intravenous infusion</i>
Morphine 0.01-0.2 mgkg-	1 0.01-0.02 mgkg-1hr-1
Pethidine 0.1-1.0 mgkg-	1 0.1-0.2 mgkg-1hr-1
Fentanyl 1-5 mcgkg-1	0.5-2.0 mcgkg-1hr-1
Tramadol 0.5-1.0 mgkg-	1 0.1-0.2 mgkg-1hr-1

The intravenous route has the advantage of producing prompt and predictable blood levels. This route allows precise titration of analgesic requirements to the needs of the patient. Once adequate analgesia has been obtained with IV boluses, maintenance can be achieved by IV or SC infusions.

The intravenous route is used in postoperative intensive care units or high dependency units to obtain rapid control of pain. It is also the preferred route in patients who are hypotensive or hypovolaemic as it produces instantaneous and predictable therapeutic blood levels. While continuous infusions provide a steady blood level, it must be remembered that it may take up to 5 half lives of a drug (20 hours in the case of morphine) to achieve 95% of the final steady state concentration. Thus, inadequate analgesia in a patient receiving an IV infusion is best dealt with by IV boluses rather than by increasing the infusion rate of the drug.

Transdermal Route.

Transdermal drug delivery allows continuous parenteral administration of drug without the need for needles or infusion devices. Lipid-soluble drugs such as fentanyl are suitable. Transdermal fentanyl patches are available with different delivery rates ranging from 25 to 100 micrograms/hour. Currently available patches have a slow onset and offset of action and absorption continues for up to 72 hours while the patch is in place.

Limitations include the slow onset and offset times due to the formation of a significant transdermal 'reservoir', which makes short-term titration impossible. These factors make transdermal fentanyl patches unsuitable for acute pain management and are currently restricted to chronic and cancer pain treatments.

Adverse effects of opioids (4).

Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. Clinically meaningful adverse effects are dose-

related. Once a threshold dose is reached, every 3-4 mg increase of morphine-equivalent dose per day is associated with one additional adverse event or patient day with such an event.

Respiratory depression is the most feared side effect that can usually be avoided by careful titration of the dose against effect. The majority of studies investigating opioid related hypoxia in the postoperative period have found that measurement of respiratory rate as an indicator of respiratory depression is of little value as hypoxaemic episodes often occur in the absence of low respiratory rate. As respiratory depression is almost always preceded by sedation, the best early clinical indicator of drug accumulation/respiratory depression is increasing sedation.

Supplemental oxygen for 48 hours following major surgery is beneficial, particularly in elderly and high risk patients, because of the link between postoperative hypoxaemia, tachycardia and myocardial ischaemia.

Postoperative nausea and vomiting (PONV) are very common adverse effects of opioids. The risk is significantly reduced by the use of droperidol, dexamethasone and ondansetron, all of which are equally effective. Omission of nitrous oxide and the use of total intravenous anaesthesia using propofol are less effective in decreasing the incidence of PONV.

Opioid induced pruritus is usually treated with naloxone, naltrexone and droperidol. Minimum effective doses of these drugs are not yet known.

Patient Controlled Analgesia (4), (5).

Patient controlled analgesia (PCA) is a technique wherein patients self-administer small doses of an analgesic agent (usually by the IV or SC route) when they experience pain. This technique not only gives patients control over their pain, but also overcomes some of the problems associated with pharmacodynamic and pharmacokinetic variability among individual patients.

Most intravenous-PCA (IV-PCA) devices consist of a microprocessor-controlled pump triggered by pressing a button. When triggered, a preset amount (incremental dose) of drug is delivered intravenously. A timer in the pump prevents administration of an additional bolus until a specified period (lockout interval) has elapsed. Thus, individual patients can titrate opioids to their own needs within the boundaries of safety drawn by the anaesthetist. The incremental doses and lockout periods for some of the commonly used opioids for patient controlled analgesia are given in table 2.

Table - 2 : Guidelines for patient controlled intravenous opioid administration.

Drug Demand (concentration) dose	Lockout interval (minutes)	Continuous basal infusion
Morphine (1 mgml-1) 1–2 mg	5–10	0 – 2 mghr-1
Pethidine (10 mgml-1)* 10–20 mg	5–10	0 – 20 mghr-1
Fentanyl (10 mcgml-1) 20- 50 mcg	5–10	0 – 60 mcghr-1
Sufentanil 4–6 mcg	5–10	0 – 8 mcghr-1
Tramadol 10–20 mg	5–10	0 – 20 mghr-1

*Only if patient is intolerant to all other opioids.

Adequate analgesia can be established by titrating intravenous loading doses prior to starting patient controlled opioid administration. Elderly or compromised patients may need smaller doses of opioids.

Most PCA pumps provide the option of adding a continuous background infusion to the basic patient controlled mode. This technique has the advantage of providing more controlled blood levels and improved analgesia (especially during sleep) with fine-tuning of opioid requirements being done by the patient. Disadvantages include difficulty in predicting optimal background infusion rate (resulting in a possible overdose in some individuals) and loss of one of the safety features of the PCA technique because sleeping patients can continue to receive medications irrespective of their needs. Background infusion is now not recommended in adults for routine use; however, it may be useful in opioid-tolerant patients.

When IV access is difficult to obtain, PCA can be administered through the SC route. A standard PCA pump attached to an administration set can be used to deliver the drug into the SC plane through a cannula or a butterfly needle. The drug concentration is usually increased 5-fold to avoid administration of large volumes of fluid into the subcutaneous plane.

Patient controlled epidural analgesia (PCEA) is the second most commonly used route of PCA delivery for acute pain management. The advantages provided included superior analgesia, increased patient satisfaction and decreased side effects. Optimal PCEA variables have not been clearly determined. For postoperative analgesia, 2 to 4 ml of 0.0625% to 0.25% bupivacaine with a lockout interval of 10 to 20 minutes and a continuous infusion of 3 to 10 ml/hr is

commonly used. Continuous infusion has been recommended with PCEA to optimise the potential physiological benefits of epidural analgesia and maintain continuous neural blockade. Combining a lipid soluble opioid provides superior analgesia.

Other routes of PCA delivery include oral PCA, intranasal PCA (PCINA), transdermal PCA and regional PCA (PCRA).

Neuraxial analgesia.

Intrathecal opioids (6).

Intrathecal opioids are now widely used alone or as useful adjuncts in treatment of acute pain. Within the spinal cord, they bind to specific receptors in the dorsal horn. Combining low doses of opioids with local anaesthetic agents for intrathecal administration has shown to increase the speed of onset, density of block and the duration of analgesia.

High lipid solubility of opioids such as fentanyl and sufentanil accounts for minimal rostral spread, relatively small dermatomal band of analgesia and limited duration of action unlike hydrophilic opioids such as morphine which have a greater degree of rostral spread, delayed respiratory depression and extensive dermatomal analgesia. Recent studies have shown that intrathecal administration of lipophilic opioids can also result in respiratory depression that occurs in the first 20-30 minutes after injection. This is due to the rapid distribution of the drug in the cerebrospinal fluid. However this effect lasts only for a few minutes unlike morphine which peaks by approximately 6 hours and persists for about 18-24 hours.

Internationally, opioids and adjunct analgesics are supplied as preparations that include preservatives. Benzyl alcohol and the parabens have been implicated as a cause of neurotoxicity after intrathecal administration and hence are to be avoided. The pharmacological properties of commonly used intrathecal opioids is summarised in table 3.

Table - 3 : Pharmacologic properties of common opioids used for intrathecal analgesia.

Opioid	Usual dose range(mcg)	Onset(min)	Duration(h)
Morphine	100 - 500	45 - 75	18 – 24
Fentanyl	5 – 25	5 – 10	1 – 4
Sufentanil	2.5 – 10	5 – 10	2 – 6

Side effects of intrathecal opioids include pruritus, nausea and vomiting, urinary retention and respiratory depression.

Epidural analgesia (7).

The epidural route is more popular for postoperative pain management as the technique can be used alone or in combination with general anaesthesia. Epidural technique has been found to provide better pain relief than systemic opioids and also decreased incidence of postoperative complications. Lumbar epidural catheters can be kept in place for prolonged periods. Epidural catheter placed in a location congruent to the incisional dermatome has been shown to provide superior analgesia. Segmental analgesia for upper abdominal surgery can be obtained by placing the catheter at T8 to T10 levels. Morphine administered in the lumbar region can provide good postoperative analgesia for upper abdominal and thoracic surgeries as well. The hydrophilic nature of morphine results in its rostral spread, making it possible to obtain good pain relief for upper abdominal and thoracic procedures following administration through a catheter placed in the lumbar region. Fentanyl, on the other hand, is lipophilic and hence needs to be administered close to the segmental level where analgesia is required. Morphine has a slower onset of action as compared to fentanyl. In addition, fentanyl tends to produce a more definable segmental block as compared to morphine. The initial bolus dose of morphine is in the range of 1 to 6 mg, followed by an infusion at a rate of 0.1 to 1.0 mg/hr. The bolus dose produces analgesia within 30 minutes and the effect lasts for 6 to 24 hours. Fentanyl in a bolus of 25 to 100 micrograms produces analgesia in 5 minutes, the effect lasting for up to 1.5 to 3 hours. The rate of infusion of fentanyl is 25 to 100 micrograms/hour. Elderly patients need much lower doses of drugs to produce effective analgesia. The effective total dose of epidural morphine needed in 24-hours can be predicted by the formula:

Effective 24-hour epidural morphine dose (mg) = $18 - (\text{age} \times 0.15)$.

Opioids can either be administered alone or in combination with 0.0625-0.125% bupivacaine. When opioids are being administered by the epidural or subarachnoid route, concurrent systemic use of other opioids or sedatives must be avoided. Patients should be closely monitored for systemic effects of opioids such as decreased respiratory rate or excessive sedation. When combined with local anaesthetics, one should in addition monitor haemodynamics and motor blockade.

DepoDur™ is a novel analgesic formulation of morphine for postoperative pain management intended for epidural administration. It consists of morphine encapsulated within liposomes to provide extended release of the drug. DepoDur™ given as a single epidural injection before surgery has been shown to produce pain relief for up to 48 hours.

Nonopioid analgesic techniques (8).

An increasing number of complex surgeries are performed on an outpatient basis for which the use of IV-PCA, spinal or epidural analgesia are not practical pain management techniques. Extensive use of perioperative opioids is associated with side effects such as PONV, pruritus, urinary retention and paralytic ileus. Nonopioid analgesic techniques have thus emerged as adjuncts for

perioperative pain management. These techniques are incorporated as a part of multimodal or balanced analgesia techniques.

Local anaesthetic techniques.

Local infiltration of incisions with long acting local anaesthetics, peripheral nerve/plexus blocks, and continuous neuraxial blocks can provide effective and safe analgesia into the postoperative period. In addition, use of these can decrease the incidence of PONV. Infiltration of 0.25% bupivacaine along surgical incisions provides effective analgesia for several hours. In a similar manner, regional techniques that can be recommended include interscalene block for shoulder surgery, sciatic and femoral nerve block for surgery on the lower limb, intercostal block for thoracic and upper abdominal procedures, and interpleural analgesia for surgery on gall bladder and kidney (unilateral). The disadvantage of local anaesthetic techniques is that they are effective only for 6-8 hours. Pain control can be improved by the use of continuous techniques for local anaesthetic (LA) infusion. Long acting LA suspensions and delayed release formulations containing liposomes / polymer microspheres may minimise the need for continuous catheter delivery systems in the future.

Nonopioid analgesics.

Though opioids by several routes have been the mainstay of pain management techniques, they do not provide the complete solution in patients experiencing severe postoperative pain. Addition of a non-sedating, non-opioid analgesic to an opioid is now a popular multimodal form of therapy that provides superior analgesia to either drug alone. While non-opioid analgesics serve as good therapeutic adjuncts to opioids in the first 24 to 48 hours, they can be used as sole analgesics beyond 48 hours.

Nonsteroidal antiinflammatory drugs (NSAIDs) such as acetaminophen, ibuprofen, ketorolac, diclofenac and COX-2 inhibitors are popular drugs used for this purpose. These drugs are administered by the oral, rectal or intramuscular routes to supplement an opioid-based analgesia. They are often administered along with premedication in the technique termed “preemptive analgesia”. While traditional NSAIDs such as acetaminophen, ibuprofen, ketorolac and diclofenac inhibit both COX-1 and COX-2 forms of the cyclo-oxygenase enzyme, newer NSAIDs inhibit the inducible form of the enzyme, the COX-2 enzyme, which is released following surgical trauma, sepsis and hypoxia.

Paracetamol is used in clinical practice as an effective analgesic and antipyretic. It acts by inhibiting central cyclo-oxygenase-2 (COX-2) in the central nervous system. It also inhibits the putative central ‘COX- 3’ that is selectively susceptible to paracetamol. It modulates the inhibitory descending serotonergic pathways and prevents prostaglandin production at cellular transcription level. Paracetamol given alone is effective for mild to moderate pain. It is a useful adjunct to opioids in more severe pain. It is used orally in doses of 10-15 mg/kg every 4 to 6 hours with a maximum dose not exceeding 90 mg/kg/day. Single oral doses in excess of 90 mg/kg can result in severe liver damage and acute tubular necrosis. The drug can also be given rectally in an initial dose of 35-40 mg/kg, followed by 20 mg/kg every 6 hours. Intravenous paracetamol preparations are as effective as ketorolac and as equivalent to morphine after surgery.

Oral ibuprofen in a dose of 6-10 mg/kg-1 6th hourly is known to produce a 30% reduction in opioid requirements.

Intramuscular ketorolac (10 and 30 mg doses) has been found to be as effective as IM morphine (12 mg) for relieving pain on the 1st and 2nd postoperative days following major surgery. A study on patients undergoing cholecystectomy revealed that morphine (10 mg IM) provided superior analgesia when compared to Ketorolac (30 mg IM). The usual dosing regimen for ketorolac is 30 mg IM initially, followed by 10 mg IM 6th hourly, for a maximum of 3 days. Care is to be taken when dosing the elderly and those with renal impairment.

Diclofenac can be given by rectal or IM routes as adjuncts to opioid medications in the management of postoperative pain. While rectal suppositories are available in strengths of 12.5, 25, 50 and 100 mg, the intramuscular preparation is available as 75 mg/3 ml ampoule.

COX-2 inhibitors such as rofecoxib and valdecoxib are available for oral administration. These drugs are administered orally as preemptive analgesics along with premedication. Parecoxib, a prodrug of valdecoxib, is the only injectable COX-2 inhibitor available. It is administered as a one-off perioperative dose.

On the basis of current evidence, NSAIDs are not sufficiently effective as sole agents for providing pain relief following major surgery though they may be effective following minor or moderate surgery. When combined with opioids, they decrease opioid requirements and also minimize opioid-related adverse effects. They occasionally increase bleeding time and can result in increased blood loss. But a recent systematic review of literature suggested that evidence supporting bleeding tendency was equivocal at best. COX-2 inhibitors have been found to have a negative influence on bone growth. Hence, COX-2 inhibitors are not to be used for more than 3 to 5 days following surgery.

Analgesic adjuncts (9).

NMDA antagonists: Ketamine, dextromethorphan, magnesium and adenosine have been tried as analgesic adjuncts for postoperative pain management. These have been shown to inhibit the receptor-gated calcium currents that amplify neuronal firing. Ketamine has been shown to be a useful adjunct when given as an IV bolus, continuous IV infusion (0.5 mg/kg/hr to 20 mg/hr) or epidural infusion (0.25 mg/kg/hr) without any increase of adverse CNS effects.

α₂ agonists : Low dose clonidine has proved to be a useful adjunct analgesic when given neuraxially (150 mcg intrathecally or 2-3 mcg/kg epidurally), and in combination with peripheral nerve blocks (0.5 mcg/kg). Higher doses are associated with adverse effects such as sedation, bradycardia and hypotension and should be avoided.

Neostigmine: Intrathecal administration of 25-100 mg neostigmine has been associated with high incidence of nausea and vomiting, bradycardia, hypotension, sweating, agitation and distress.

Hence, it is not recommended for intrathecal use. Neostigmine is being investigated as an analgesic adjunct for intra-articular and epidural use.

Naloxone, *corticosteroids* and *gabapentine* are other drugs being investigated for use as analgesic adjuncts.

Pain management in special groups.

Pain management in children (10).

Children constitute a special category of patients needing specific considerations for postoperative pain management. Children feel pain and remember pain, just like adults. Pain in children produces similar deleterious physiological and psychological effects. This is true for neonates and preterm infants as well.

Assessment and treatment of pain presents problems in the paediatric age group because of developmental, cognitive and emotional differences. Alternate routes of drug administration such as the sublingual, rectal and transdermal routes are more popular.

Opioid clearance is prolonged in the neonate and the older infants. This makes the paediatric population more prone to the respiratory depressant effects of opioids.

Caudal epidural is a popular route for providing pain relief for lower abdominal, lower limb and perineal procedures. The Armitage formula (table 4) may be employed to calculate the dose of drug for caudal analgesia. (11)

Table - 4 : Dose requirements for caudal analgesia in children (from Armitage1)

Site of surgery	Dose of drug * (0.25% bupivacaine)
Lower limb/perineal (below T12)	0.5 ml/kg
Lower abdominal (between T10-T12)	1.0 ml/kg
Upper abdominal/thoracic (above T10)	1.25 ml/kg

* If the total predicted volume of 0.25% bupivacaine exceeds 20 ml, the concentration of bupivacaine is reduced to 0.1875%

Other regional techniques can also be used for providing excellent pain relief in children.

- Block of the dorsal nerve of penis or application of lignocaine jelly can provide postoperative analgesia following circumcision.

- Block of the iliohypogastric and ilioinguinal nerves provides excellent pain relief following herniotomy and orchidopexy.

- Infraorbital nerve block provides exemplary pain relief following cleft lip surgery.

NSAIDs by oral, rectal or parenteral routes are useful in providing preemptive analgesia in children. However, like in adults, these are best considered as adjuncts rather than primary agents for pain management. NSAIDs have similar adverse effect profiles in children as in adults. Oral paracetamol is used in a dose of 15 mg/kg every 6 hours with the maximum daily dose not to exceed 90 mg/kg in otherwise normal children. The maximum daily oral dose of paracetamol should not exceed 75 mg/kg in term neonates or 40 mg/kg in premature less than 32 weeks. Rectal paracetamol is used in an initial dose of 30 mg/kg followed by 20 mg/kg every 6 hours.

Oral ibuprofen is used in a dose of 10 mg/kg-1 every 6 to 8 hours. Oral diclofenac is used in a dose of 0.5-1.0 mg/kg every 8 hours. Rectal suppositories of diclofenac are also available.

Intramuscular ketorolac is administered in a dose of 0.25-0.5 mg/kg every 6 hours.

Pain management in elderly

Advances in anaesthetic and surgical techniques means that increasingly elderly patients are undergoing more major surgeries. Factors that can combine to make effective control of acute pain in the elderly more difficult include a higher incidence of co-existing diseases and concurrent medications (which increases the risk of drug-drug and disease-drug interactions); age-related changes in physiology, pharmacodynamics and pharmacokinetics; alteration of responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment.

Alteration in pharmacokinetics and pharmacodynamics of drugs mandate the decrease in bolus and infusion doses of opioids; and the need to titrate and continuously monitor the patient for overdose.

Due to sensory neuronal degeneration and neurochemical changes associated with aging, elderly patients have a higher pain threshold. But, their ability to tolerate severe pain is limited and physiological changes such as hypertension and tachycardia can be detrimental. Delirium is a common form of cognitive impairment in the elderly in the postoperative period. They may need more time to understand and respond to questions regarding pain. Verbal descriptive scale (VDS) has shown to be a more reliable measure of pain than the VAS or NRS (numerical rating scale) in the elderly.

It is safer to employ a combination of pharmacological and non-pharmacological techniques of pain relief in the elderly.

NSAIDs and Paracetamol: Elderly are more likely to suffer adverse gastric and renal side effects following administration of NSAIDs. Renal failure is of particular concern as they are more likely to have pre-existing renal impairment. Selective COX-2 inhibitors have significantly lower incidence of gastrointestinal complications and have no antiplatelet effects. However, the incidence of renal side effects is similar to nonselective NSAIDs. Paracetamol has proved to be safe and there is no need of dose reduction in the elderly.

Opioids : Elderly patients require less opioid than younger patients. However, a large interpatient variability still exists and doses must be titrated to effect in all patients. Morphine and fentanyl requirements are decreased two- to four-fold. Elimination half lives of opioids are prolonged and rapid accumulation of metabolites such as morphine-6-glucuronide or norpethidine can occur because of reduced renal function. Sedation occurs earlier than respiratory depression. Hence, the doses must be titrated under close monitoring.

The incidence of pruritus, nausea and vomiting is less in the elderly. PCA is an effective method of postoperative analgesia with better patient tolerance, decreased confusion and decreased incidence of pulmonary complications.

Local anaesthetics : Elderly patients are more sensitive to the action of local anaesthetic agents because of slowing of conduction velocity of neurons and decrease in the number of neurons. The duration of epidural and subarachnoid block is prolonged. When local anaesthetics and opioids are used in combination for continuous epidural techniques for postoperative pain relief, age-based doses or infusion rates are recommended. The elderly individual is susceptible to hypotension during neuraxial analgesia.

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PERI OPERATIVE FLUID AND GLUCOSE THERAPY IN CHILDREN

Introduction.

The aim of peri operative fluid management is to maintain haemodynamic stability and haemostasis by providing adequate intravascular volume, cardiac output and as a result, tissue oxygenation during times of surgery and anaesthesia induced physiological stress. Intravenous fluid therapy regimes in children undergoing surgery must account for different fluid requirements: fluid deficits (fasting), maintenance fluid requirements (gastrointestinal (GIT)/renal and cutaneous losses), third space losses and haemorrhage.

The role of glucose supplementation is to provide sufficient energy to prevent hypoglycaemia during starvation and the peri operative period.

This review will focus on peri operative maintenance fluid therapy.

Historical review.

Maintenance therapy is defined as the provision of fluid and electrolytes to replace the anticipated physiological losses secondary to insensible losses (breathing/sweating/from GIT) and urine output, in a normal individual over a 24 hr period.

In 1957, Holliday and Segar developed a formula to estimate the total caloric expenditure of hospitalised children from their body weight [1]. They calculated the metabolic rate of healthy children at rest and during activity. As the maintenance needs for water paralleled energy metabolism, then the estimated caloric expenditure was used to determine the maintenance fluid therapy (1 ml of water required/each calorie consumed). In the same study, the maintenance electrolyte needs were calculated from the amount of electrolyte delivered by the same volume of human milk. The impact of Holliday and Segar's paper was considerable. Their recommendation (with minor modifications), best known as the "four-two-one of four and a fifth" rule, that is hourly maintenance requirements of 4 ml/kg of fluid per kg for the first 10kg of a child's weight, 2ml/kg for the next 10 kg and 1ml/kg thereafter; the fluid consisting of 0.18% saline in dextrose 4% solution – has lasted 50 years in paediatric medicine, particularly in paediatric anaesthesia [2]. Over the years, other hypotonic solutions (eg. 0.2 – 0.25% saline in dextrose 5 or 10%) have also come into common use. Adding sufficient dextrose to render the solution iso-osmolar allows the solution to be given painlessly into a peripheral vein and the theoretical protection against hypoglycaemia has been cited as another reason for using dextrose-saline as maintenance in children [3]. *However iso-osmolar dextrose-saline, which (as the dextrose is metabolized in vivo) is effectively hypotonic.*

The traditional use of hypotonic maintenance fluid in paediatric medicine is based on requirements of *normal physiology* and it has served the vast majority of children well due to the fact that healthy or near healthy children are able to excrete large volumes of free water in the urine. In recent years, many authors have started to question the safety of hypotonic solutions in

the paediatric population in the peri operative setting. A significant number of case reports of severe hyponatraemia, encephalopathy and brain injury associated with traditional fluid therapies have appeared in the medical literature [4, 5, 6, 7, 8, 9]. There is now evidence to show impaired free water clearance in children post surgery and during severe infections [10, 11]. These findings imply that intravenous therapy at maintenance rates with hypotonic saline solutions in the peri operative period put children at risk of hyponatraemia and encephalopathy – the syndrome of water intoxication.

The original purpose of adding glucose to the IV fluids was to provide adequate energy to prevent hypoglycaemia during starvation and the peri operative period. It was thought that children deprived of oral intake by preoperative fasting were at greater risk of hypoglycaemia, because they lack the glycogen stores of adults. But numerous studies since the 1980s have demonstrated that in normal children, including infants below 1 yr of age, hypoglycaemia is not a common occurrence in the peri operative period [15, 16, 17, 18]. Children, like adults, generally show an increase in blood glucose levels in the morning and to stress (starvation and surgery), which includes hyperglycaemia even when no dextrose containing fluids are given [17]. Administration of glucose during anaesthesia and surgery can lead to intraoperative hyperglycaemia which is undesirable. Hyperglycaemia can induce diuresis and consequently dehydration and electrolyte disturbances, especially in small preterm infants with immature tubular function [19]. Moreover, several studies have demonstrated hyperglycaemia will increase the risk of hypoxic-ischaemic brain or spinal cord damage, wound infection and delays healing [20, 21]. Exceptions to the above suggestions are neonates in the first 48 hrs of life, infants of diabetic mothers, infants with intrauterine growth retardation, those in whom a glucose infusion has been interrupted or children receiving total parenteral nutrition (TPN). These children may require glucose infusions to prevent hypoglycaemia in the peri operative setting and dextrose 5% infusion at 4 ml/kg/hr may be sufficient [22].

So, Holliday and Segar's recommendation of using "four and a fifth" is not even close to the ideal maintenance solution in children, yet it continues to be the most widely prescribed fluid in paediatric peri operative period [4].

Physiology of sodium & peri operative hyponatraemia.

Sodium is the main cation of extracellular fluid (ECF). Changes in the blood sodium concentration mirrors ECF volume changes. As water moves freely across the cell wall, water movement across membranes will follow the variations of the effective osmolality (tonicity) in the intracellular fluid (ICF) and the ECF. Hyponatraemia produces osmotic movement of water across membranes from the EC to IC space.

In the brain, the endothelial tight junctions prevent sodium moving across the blood-brain barrier. Normally, there is equilibrium between the tonicity of the brain IC and EC spaces. When there is an acute decrease in serum osmolality, as in hyponatraemia, there is a shift in water from the EC space to the brain cells, in attempt to lower the brain osmolality and to match that of hypotonic plasma.

Children are more susceptible than adults to the effects of hyponatraemia. They have a larger brain to intracranial volume ratio compared to adults and thus, there is a greater increase in intracranial pressure for any given increase in brain volume. In animal studies, in the presence of hyponatraemia post-pubertal animals show an adaptive mechanism whereby sodium is extruded from brain cells using a $\text{Na}^+ - \text{K}^+$ ATPase mechanism. In prepubertal rats and new born dogs the activity of this enzyme is much lower, reflecting a limited ability to extrude sodium from the brain cells and as a result, greater vulnerability to hyponatraemia [12]. This finding may explain why the clinical symptoms of hyponatraemic encephalopathy occur earlier in children than adults. The average sodium concentration in children with hyponatraemic encephalopathy is 120 mmol/L, while the concentration in adults is 111 mmol/L. In children deaths have been reported with sodium concentrations of 128 mmol/L [5].

The most important physiological factor in the development of hyponatraemia in the peri operative child is antidiuretic hormone (ADH). ADH is important for the maintenance of osmotic homeostasis, as well as for the maintenance of blood volume and blood pressure. A number of factors associated with surgery (bleeding, pain, stress, nausea, opioids, non steroidal anti-inflammatory drugs etc) are accepted as triggers for non-osmotic (or inappropriate) secretion of ADH. Inappropriate ADH secretion is an elevated ADH secretion in the absence of a hypovolemic or hypertonic state, or a normal secretion of ADH associated with an abnormally high sensitivity of the distal renal tubules and collecting ducts to ADH. It is characterized by hyponatraemia and oliguria, while the haemodynamic status is normal. This syndrome is often seen in the post operative setting in both minor and major surgery [13, 14] and normal ADH levels may return only after 2 or 3 days.

The most important pharmacologic factor in the development of peri operative hyponatraemia is the formulation of the intravenous fluid that is given. As mentioned earlier, children are traditionally prescribed iso-osmolar dextrose-saline, which (as the dextrose is metabolized *in vivo*) is effectively hypotonic. This practice is still common in the anaesthetic community, because the predicted maintenance requirements of water and sodium are met by this solution.

Current trends in paediatric fluid therapy.

With the reporting of numerous cases of severe hyponatraemia in children given hypotonic fluids, conflicting approaches have been suggested to prevent this hyponatraemia. In a recent editorial in the BJA [4], these controversies were highlighted and two schools of thought were discussed. The first is that we should continue prescribing dextrose-saline but less of it, while the second is that there should be a wholesale move to the prescription of isotonic maintenance fluids. The following paragraphs are direct quotes from the BJA editorial.

The argument for lower volume but continued hypotonic replacement is: “The fluid requirements overall have been overestimated; fluid losses are made up of two components – an electrolyte free insensible loss and an electrolyte containing urinary loss. Losses from both components have been over estimated but it is the renal loss that is affected by the action of ADH; thus overall less

replacement fluid is required but there is a need for some of this replacement to be “free water” – hence we should continue to prescribe hypotonic fluids at volumes of about 60% of current values [7]”.

“The argument against this approach for the paediatric surgical patient is that it presupposes that any hypovolaemia or other ongoing losses are separately accounted for – using colloid or isotonic crystalloid for hypovolaemia and some matched solution as isovolaemic replacement for ongoing losses (eg. drains, GI tract). This counsel of perfection may, of course, be the case, but if it is not then any degree of hypovolaemia is perpetuated. Indeed, the temptation to use one fluid for maintenance, surgical loss replacement and as volume therapy for anaesthesia induced hypotension almost certainly explains those reports of death and brain injury when volumes of hypotonic fluid based on Holliday and Segar’s formula have been given”.

“What if children were to be given isotonic maintenance fluid? It is argued that if maintenance fluids were to be given as saline 0.9% at the current recommended volumes then this should remove the danger of hyponatraemia from most patients. It would mean that children would receive a large (5-fold) increase in sodium intake and potentially many more children would develop some degree of hyperchloraemic acidosis. Using Hartmann’s solution instead might avoid this problem. Either saline 0.9% or Hartmann’s solution could be presented with dextrose in circumstances where hypoglycaemia was perceived to be a potential risk. The electrolyte load could be decreased by giving smaller volumes of isotonic maintenance fluid than currently recommended. The potential problems with such an approach are that it would expand EC space in all cases and this might be very disadvantageous to certain ill children. Also, it gives no free water.

This whole notion that giving isotonic fluids would provide a guarantee against hyponatraemia has been questioned. In women undergoing gynaecological surgery and receiving only near isotonic peri operative fluids, sodium concentrations in the first 24 – 36 hrs after surgery were shown to be reduced.

During this time, these patients pass relatively large volumes of urine that is hypertonic to their serum - that is their kidneys generate free water. The explanation of this is thought to be that expansion of the EC space by the isotonic fluid they receive induces naturesis at a time when the raised ADH levels from surgical stress prevents the kidneys from diluting the urine – a process that has been labelled desalination [23].

Possible solutions and practice tips.

In this position of uncertainty, more research trails need to be done to get a definitive answer to the question of “what is the ideal IV fluid in the peri operative paediatric setting?”

Most investigators, and Holliday and Segar themselves, recognise that it is necessary to reduce the maintenance fluid volume to 50% of the classical recommendations in the post operative period. They suggested correcting fluid losses promptly with 20-40 ml/kg of normal saline, particularly

during surgery and also halving the average maintenance fluid (50 ml/kg/day) for the first day of infusion and monitoring sodium concentrations daily if IV fluid therapy is to be continued [24].

Some investigators have suggested that isotonic saline in 5% dextrose in water to be the safest fluid composition in most children and also advocate monitoring sodium concentration before and after commencing IV fluid therapy [25, 26]. For Duke and Molyneux, if the use of isotonic solution does not rule out the risk of hyponatraemia, it decreases the probability of occurrence. They suggest the use of isotonic saline with 5% dextrose, at a maintenance rate less than usual recommendations (60-70% of usual recommendations), in children with sodium concentrations less than 138 mmol/L and those at risk for non-osmotic secretion of ADH [8].

For normal children undergoing surgery, Welborn has suggested using normal saline with dextrose 2.5% on the basis that using this solution provides the necessary electrolyte and free water replacements and a consistent increase in blood glucose without the moderate to marked hyperglycaemia that can be seen with isotonic solutions with 5% dextrose [27]. In the UK, both 0.9% and 0.45% saline solutions with 2.5% dextrose are available. However, solutions containing 2.5% dextrose or less may not be available in some places. One practical approach is glucose solution administered at a desired delivery rate of glucose (mg/kg/hr) to prevent hypoglycaemia and balanced salt solution as a replacement fluid. Glucose infusion at a rate of 120 mg/kg/hr is sufficient to maintain an acceptable blood glucose level and prevent lipid mobilisation and ketosis in infants and children [28].

It should be remembered that these are only guidelines. The issues of what fluid, how much and how fast are interdependent. Safe resuscitation requires close observation of the cardiovascular system, conscious state, and urine output and blood chemistry. When close biochemical monitoring is not possible, as in the developing world, a fluid regime should be chosen which is least likely to cause biochemical changes.

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PERIOPERATIVE FLUID AND TRANSFUSION THERAPY IN TRAUMA

Introduction.

Tissue injury from trauma results in a systemic inflammatory response, secondary to the release of mediators resulting in increased vascular permeability and tissue oedema. In addition, a concurrent haemorrhage causes further reduction in intravascular volume. The initial fluid redistribution that occurs following trauma is related more to the degree of tissue trauma and ischemia than to blood loss per se. With mild hypovolemia, blood in the venous capacitance vessels is mobilised to ensure adequate venous return. When this is depleted, fluid from the interstitial space is shifted to the intravascular space (autotransfusion) and the gradient between the oncotic pressure and hydrostatic pressure decreases. If there is further blood loss, haemorrhagic shock results. A decrease in cardiac output and arterial O₂ content leads to decreased O₂ delivery. Cellular mechanisms fail, sodium potassium adenosine pumps fail, causing water to shift into the intracellular space further depleting intravascular fluid, cellular swelling occurs and ultimately cell death if the process is not reversed.

Aim of fluid resuscitation.

One third of trauma deaths are due to haemorrhage and hypotension. Resuscitation in the hypovolemic shock state is aimed at restoration of intravascular volume, normalization of impaired tissue perfusion and avoidance of complications (1). The whole goal of fluid therapy must be to ensure adequate oxygen supply but there are still many unanswered questions regarding resuscitation targets and timing, and type and volume of fluid resuscitation in trauma.

Aggressive fluid resuscitation to raise the blood pressure (mean arterial pressure) may be counterproductive. A systematic review of MAST use in trauma suggests that the risk of death is increased (2). Similarly, a meta-analysis of paramedic intervention suggests an increased risk of death (3). Colloids are effective in expanding the circulation, but there is no evidence that they improve outcome. In fact, in trauma patients without traumatic brain injury (TBI), colloids may increase mortality (4). The unifying hypothesis from these four ineffective strategies may be that raising the BP could be counterproductive, and that there may be a role for “hypotension resuscitation”. A number of studies have questioned the administration of fluids to patients with uncontrolled haemorrhage and support “hypotension resuscitation” (5,6,7). Caution needs to be used in interpreting this approach to resuscitation as the evidence to date suggests it should only be used in highly selected patients who have penetrating injuries with uncontrolled haemorrhage, where rapid transfer to the operating room is possible. Where transport times exceed 30 minutes, prehospital stabilization results in improved outcome (8,9).

The American College of Surgeons protocol for ATLS recommends replacing each ml of blood loss with 3 ml of crystalloid fluid. This is known as the 3 for 1 rule (14). The basis of the 3 for 1 rule comes from the volume of distribution of electrolyte solutions. The patient's response to this initial resuscitation determines subsequent therapy, 3 response patterns are described:

1. Rapid: Responds rapidly and remains haemodynamically stable.
2. Transient - Responds initially then deteriorates as fluids are decreased to maintenance levels.
3. Non-responsive: Failure to respond either to crystalloids or blood.

While patients should not be over resuscitated (as this is associated with increased morbidity and mortality), the evidence to date is that patients should be resuscitated to a systolic BP of 90-100 mmHg or MAP of 75-80 mmHg. If this cannot be achieved and the patient remains unstable requiring large volumes of fluid, they should be taken to the operating room for haemorrhage control (10). Failure to rapidly achieve the required intravascular volume and to improve tissue perfusion to near normal levels results in an increased incidence of ARDS, multi-system organ failure and a poorer outcome (11,12).

Choice of fluids.

Controversy persists as to the choice of the fluids for resuscitation-crystalloids or colloids? Authors have reported no difference in outcome whether crystalloids or colloids are used (except in TBI) but a combination of both may be efficacious. Again the proportion of crystalloid to colloid needed to ensure adequate volume expansion depends on the degree of permeability injury. Crystalloids expand the extracellular fluid space but larger volumes are required. It is usual practice to replace blood loss with crystalloids, using the 3 for 1 rule. Colloids by virtue of their oncotic pressure produce effective volume expansion with smaller volumes and are usually replaced at a 1 for 1 ratio.

Crystalloids can be isotonic or hypertonic. Isotonic fluids equilibrate throughout the intravascular and interstitial compartments but do not cause intracellular shifts. These can effectively replace interstitial fluid shifts. Hypertonic fluids can cause redistribution of intracellular fluid into extracellular compartments but it is mainly from the interstitial space.

The theoretical advantage of using hypertonic fluids is mainly the small volume requirements for resuscitation. The osmotic effects, the inotropic effects and the direct vasodilatory effects of hypertonic saline leads to increase in MAP, cardiac output and an increase in renal, mesenteric, splanchnic and coronary blood flow with the peripheral vasodilatation. But to be effective, studies have shown these solutions must pass through the lungs, thus stimulating osmolar receptors but hypertonic saline can also predispose to increased haemorrhage from the open blood vessels. The vasodilatory effect can counteract the early compensatory vasoconstrictor response induced by hypovolemia. It can also cause hyponatremia and hyperchloremia with a resultant metabolic acidosis. The serum levels are relatively normal with small infusions.

Blood substitutes were developed in the search for a non- antigenic disease-free, oxygen-carrying fluid. Three haemoglobin-based products are available, stroma free haemoglobin, modified stroma free haemoglobin and liposome encapsulated haemoglobin. Other blood substitute products from outdated human blood, bovine Hb and recombinant Hb are being investigated.

The four major reasons for transfusing blood and blood products in trauma are (1) improvement of oxygen transport, (2) restoration of red cell mass, (3) correction of bleeding caused by platelet dysfunction and (4) correction of bleeding caused by factor deficiencies.

Massive transfusion.

Transfusion of at least one blood volume or 10 units of blood in a 24 hr period is a massive transfusion. In 1982, Millers study on trauma patients reported that in those receiving more than 40 units within the first 24 hrs had a survival rate of less than 15%, those from 30-39 units had a 40% survival rate and those receiving between 20-29 units had a survival rate of 69%. Survival has been reported even with 100 units of blood and the current survival rate following massive transfusion is 50%.

Partial cross matching and uncross matched blood are essential considerations according to the type of trauma. Only about 1 in 800 people have an unexpected serum antibody during cross match and only 1 in 2500 have antibodies capable of causing hemolysis. If for some reason, more than 4 units of type 'O' Rh negative packed red blood cells (PRBCs) have been given, its best to switch over to type specific blood when it becomes available because the high anti -A, anti -B titres could cause hemolysis of type specific donor blood. O (-ve) whole blood should not be given as the high donor anti-A and anti-B titres could cause hemolysis of recipient RBCs.

Salvage of shed blood from wounds, body cavities, and drains finds use in trauma patients. The blood can be directly anticoagulated and reinfused into the patients using a macro-aggregate filter. Another method is the use of a cell-saver and provision of washed red blood cells. Several complications can occur and is usually seen with autotransfusion of more than 1500ml of shed blood.

Massively transfused patients require transfusion of specific hemostatic components, platelets, frozen plasma, cryoprecipitate. The American Society Of Anesthesiology Task Force on blood component therapy gives recommendations for specific therapy (13). The following passages include summaries and direct quotes from the latest ASA recommendations of 2006.

In trauma settings when massive blood loss is involved and or when organ ischaemia is suspected, haemoglobin (Hb) or haematocrit must be measured. PRBCs should usually be administered when Hb concentration is low (eg. less than 6g/dl in a young health patient), especially when the anaemia is acute. PRBCs are usually not needed when the Hb concentration is more than 10g/dl. These thresholds may be altered in the presence of anticipated blood loss. The determination of whether PRBCs are needed when Hb concentration is between 6 – 10 g/dl, should be based on any ongoing indication of organ ischaemia, potential or actual ongoing bleeding (rate and magnitude), patient's intravascular volume status and the patient's risk factors for complications of inadequate

oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.

With massive intra operative transfusions coagulopathy is the norm. Despite a large number of clinical trials and publications in the last 10 years, the information needed to define when transfusion of a blood component should occur in the coagulopathic trauma patient is still not clear. The current ASA recommendations are that platelets should be administered when the count is below 50, 000 cells/mm³. The determination of whether patients with platelet counts between 50 – 100 cells/ mm³ require therapy, including prophylaxis, should be based on the potential for platelet dysfunction, anticipated or ongoing bleeding and the risk of bleeding into confined space (eg. brain or eye). When the platelet count cannot be done in a timely fashion in the presence of microvascular bleeding (i.e. coagulopathy), platelets may be given when thrombocytopenia is suspected.

The ASA recommends fresh-frozen plasma (FFP) is given when INR or APPT is elevated. Transfusion of FFP is not indicated if PT, INR and APPT are normal. FFP transfusion is indicated for correction of microvascular bleeding (i.e. coagulopathy) in the presence of a PT greater than 1.5 times normal or INR greater than 2.0 or an APPT greater than 2 times normal. It is to be given also in microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume (~70 ml/kg) and when PT or INR and APPT cannot be obtained in a timely fashion. FFP can also be used to correct known coagulation factor deficiencies for which specific concentrates are not available and for urgent reversal of warfarin therapy. FFP should be given in doses calculated to achieve a minimum of 30% of plasma factor concentration (usually achieved with administration of 10-15ml/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5-8 ml/kg will suffice. Five units of platelet concentrates, one unit of single-donor aphaeresis platelets or one unit of fresh whole blood provide a quantity of coagulation factors similar to that found in one unit of FFP.

The ASA recommends that cryoprecipitate be considered when fibrinogen concentrations are less than 80 mg/dL. Transfusion of cryoprecipitate is not usually required if fibrinogen concentration is greater than 150 mg/dL. Similar to platelets and FFP administration, cryoprecipitate can be considered in the setting of microvascular bleeding, where fibrinogen levels cannot be measured in a timely fashion.

The recombinant factor VII is an appropriate rescue drug when traditional, well-tested options have been ineffective. Desmopressin can also be considered in treating excessive bleeding.

End points of Resuscitation.

Control of bleeding, restoration of circulating blood volume and providing adequate oxygenation at the cellular level must remain cornerstones of care for trauma patients. No single end point has found to be sufficient by itself and these have to be considered concurrently with other vital signs. Blood pressure and heart rate are poor indicators of the severity of shock and do not correspond to the cardiac index, though these are advanced trauma life support (ATLS) guidelines. It is difficult

to monitor blood volume, cardiac index and DO₂ before and during administration of large volumes of fluids in the emergency department or operating theatre. How do we know that the patient has been adequately resuscitated? BP, HR, urine output, mental status, pulse oximeter and capnography are all used but will not reflect the situation at the cellular metabolic level. More aggressive monitors have been shown to improve mortality especially in elderly patients like the CVP, pulmonary artery occlusion pressure and arterial blood gas monitoring but studies have shown that the mean values of these are the same in the surviving and non surviving trauma patients. There are studies that show cardiac index, DO₂, and O₂ consumption as better end points following trauma. The time frame to achieve the survivor values seem to be more important than the absolute survivor values. This is probably because the patients are not allowed to go into the irreversible O₂ debt. These end points have also been questioned. Perfusion related variables such as A-V oxygen content difference, mixed venous pH, arterial base excess can also predict survival and adequacy of resuscitation. These can give some indication to the whole body O₂ debts. The mortality rate is shown to increase with the degree of acidosis at admission and the subsequent 24 hrs. Lactate levels, a measure of anaerobic metabolism correlates with survival. If the lactate level was normalised in 24 hours, there was a 100% survival rate and a 75% survival rate if it took 48 hours to clear the lactate. Gastric tonometry may provide definitive assessment of resuscitation as an indicator of restoration of splanchnic blood flow. Tissue O₂ monitoring is another good indicator. Skeletal muscle blood flow decreases early in shock states and is restored late during resuscitation, making skeletal partial pressure of O₂ a sensitive indicator of low flow. Subcutaneous tissue is another sensitive area where flow dependent O₂ consumption may be detected.

Current issues in Resuscitation.

Administration of prehospital fluids is a balance between the physiologic benefits of intravenous volume loading against time spent establishing IV access and consequences of increasing systolic blood pressure and dilution of coagulation factors. In uncontrolled haemorrhage, optimum survival is thought to be achieved by allowing blood pressure to remain low until surgical hemostasis is achieved, a technique known as 'permissive hypovolemia or hypotensive resuscitation' and systolic BP of 70-80mm Hg has been suggested. This is not appropriate for head injury patients though. Crystalloids and colloids can be used, but the colloids should be used only when BP is below 50mmHg. Aggressive resuscitation with crystalloids may increase the pulse pressure at a time when blood viscosity is decreased greatly and the clot associated with vascular injury has little time to stabilize. Stern et al compared the effects of saline resuscitation of MAP 40mmHg, 60mmHg and 80mmHg. Mortality was greater in the MAP 80mmHg group. The MAP 40mmHg had the least intraperitoneal hemorrhagic volume and lowest mortality rate but was shown to have marked metabolic acidosis and reduced DO₂. MAP of 60mmHg showed markedly improved tissue perfusion. They attained higher MAP than the aggressively treated animals and these were attributed to be changes in pulse pressure. Severe hemodilution may be a factor for increased mortality as increased CO implies increased SV and myocardial O₂ demand which all trauma patients may not be able to achieve. So normotension is not the ideal therapeutic end point. One trial in humans to test the concept of delayed resuscitation or controlled under-resuscitation showed improved survival if IV fluid administration was delayed until they reached the OR. The

death rate was found to be higher in patients who underwent immediate fluid resuscitation. The arguments against immediate resuscitation is that it reverses vasoconstriction, dislodges early thrombus when given in huge volumes, dilutes coagulation factors and changes viscosity because of the resistance to flow. So timing may be important. Optimal timing and rate of infusion are other important factors to be considered. At higher infusion rates, the blood loss is also higher. The potential risk of inducing major haemorrhage from blood vessels before surgical control could be reduced by avoiding an infusion rate that is too fast and at a very early stage of the injury. Penetrating injuries are easy to study but blunt injuries are more difficult to reproduce. Hypertonic solutions were shown to be more useful here, probably because more solutions remained intravascularly compared to the other two groups. Extracorporeal supports, heparin-bonded circuits, are all being tried. The extra corporal circuit maintain the body perfusion while isolating the vascular injuries intra operatively. As we enter the next century, resuscitation medicine remains an open field for research. Being familiar with end points of resuscitation and making interventions as and when indicated will improve outcome finally.

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