MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

Year Book 2007/2008

CONTENTS

Foreword

It gives me great pleasure to write this foreword for the second issue of the Malaysian Society of Anaesthesiologists (MSA) Yearbook 2007/2008. The MSA Yearbook is a compilation of articles to update members on the latest developments in anaesthesia, intensive care and pain management, written by our members for our members. The idea was mooted by our Immediate Past President, Dr Ng Siew Hian, and the first yearbook was published in early 2007. It generated a lot of interest and is something that our members have found useful for their practice. We have therefore continued this project, and proceeded with the 2nd issue. We hope that the Yearbook will continue to be published on an annual or biennial basis.

The Yearbook is not just a collection of articles – more importantly, it is proof of the MSA's commitment to continuing professional development for our members. The number of talks and free paper presentations made by our own members at the MSA Annual Scientific Meeting (ASM) and the National Conference on Intensive Care (NCIC) has steadily increased over the years, and the Yearbook offers the opportunity to members to write scientific papers and to share their knowledge and information with a wider audience, as only a fraction of our members are able to attend these conferences.

I wish to congratulate and thank the editor, Dr Thong Chwee Ling, who has devoted much time and energy to ensure the completion of the second issue of the Yearbook; in doing so, she has faced many challenges in getting people to firstly, commit themselves to contributing an article, and secondly, to actually submit the completed article. As in the first issue, all articles are peer reviewed and are of high standard. Without Dr Thong's persistence and perseverance, the Yearbook would not have been possible.

Syabas and thanks also goes to all our colleagues whose articles are published here; I know what kind of sacrifices of time (which may be badly needed for leisure and for sleep!) have been made in order to make this contribution. Your efforts are greatly appreciated, and I am sure all our members will benefit from your contributions.

Last but not least, to all our MSA members, I hope that you will not just appreciate and benefit from the articles contained in this volume, but that some will be inspired to become contributors in the near future.

Mary Suma Cardosa
President, MSA
April 2008

Preface

Here it is – our sophomore edition of the MSA Year Book. The editors of our maiden effort which was published last year, Dr Rafidah Atan dan Dr Nor'Azim Mohd Yunos, certainly left very large shoes to fill. However, I have endeavoured to continue their efforts to include as many members as possible. Readers will be able to find articles written (and reviewed) by seasoned practitioners who are experts in their respective area of subspecialty, as well as articles contributed by younger members of our profession.

I would like to thank all contributors and reviewers for their efforts to bring this book to fruition. I would also like to apologise for the constant 'nagging' they were subjected to in order for this collection to be published on schedule!

It is my hope that MSA will continue to support the publication of the Year Book, but this undertaking will not thrive without the support of its members. I hereby urge all members to put pen to paper (or fingers to keyboards), share their expertise and knowledge with their colleagues as well as improve their own understanding of the subject matter. May the Malaysian Society of Anaesthesiologists Year Book continue to grow from strength to strength.

Thong Chwee Ling

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Editor

Perioperative Management Of Patients With Ischaemic Heart Disease Undergoing Non-Cardiac Surgery

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INTRODUCTION

In Malaysia, Ischaemic Heart Disease (IHD) carries high mortality. In 2005, the death rates for ischaemic heart disease and myocardial infarction for Malaysia are 11.63 and 6.33/100,000 population, respectively. Furthermore, in 2006, heart disease and diseases of the pulmonary circulation was ranked second after septicemia as the 10 principle cause of death in MOH hospitals, which accounts for 15.70% of the number of deaths.[1] The figures from the United States are similar to our data.[2] IHD is the second highest cause of death after cancer (180.5/100,000 and 176.4/100,000 respectively) for the United States in 2005. It is the second leading cause of death for residents after Malignant Neoplasms (23.7 and 23.9 respectively) in the same year. These figures illustrate that IHD is a severe disease that carries a high mortality in our country and more so in a developed country such as the United States.

Not only do patients with IHD present to hospitals with medical problems related to the disease, they also present to the hospital for surgical procedures either related to the disease (e.g. percutaneous interventional procedure or coronary artery bypass grafting) or unrelated to it (e.g. laparotomy for bleeding peptic ulcer or trauma). There is no data on the incidence of IHD in the Malaysian population, therefore we cannot make any inference on the magnitude of the problem in Malaysia. However, in a study of United States Veterans presenting for intermediate – to high-risk non-cardiac surgery, 45% of that population have IHD.[3] We can only assume that the Malaysian population would be of similar, if not higher, incidence.

TABLE 1 : The incidence and mortality of perioperative reinfarction for non-cardiac surgery[4]

	TIME INTERVAL			MORTALITY OF REINFARCTION
	0 – 3 mo	4 – 6 mo	> 6 mo	
Tarhan and Moffitt (1972)	37 %	16 %	5 %	66 %
Steen and Tarhan (1978)	27 %	11 %	4.1 %	69 %
Rao, Jacobs, and El-Etr (1983)	5.8 %	2.3 %	1.5 %	36 %
Shah, Kleinman, Saml, et al (1990)	4.3 %	0 %	5.7 %	23 %

There is a myriad of publications regarding the perioperative management of such patients and it ranges from expert opinions[5-10] to guidelines from professional bodies.[11,12] Through the years there has been a change in the aim of assessment and management. Initially, the aim of assessment is to risk stratify patients and identify patients that have high risk for mortality and morbidity after undergoing the surgical procedures,[13] but now the emphasis is to assess and put in place a perioperative management of the patient to improve on the overall prognosis of the patient.[6,12] Table 2 shows the Cardiac risk indices used from 1976 until 1999. The risk indices have developed from a complicated multi variable index to a simple index as proposed by Lee et al that is currently being used in the latest ACC/AHA guidelines.[8]

TABLE 2 : The Cardiac Risk Index[8]

CARDIAC RISK INDEX WITH VARIABLES	POINTS	COMMENTS
Goldman Cardiac Risk Index, 1976[6]		
1. Third heart sound or jugular venous distension	11	Cardiac complication rate :
2. Recent myocardial infarction	10	0 – 5 points = 1 %
3. Nonsinus rhythm or premature atrial contraction on ECG	7	6 – 12 points = 7 % 13 – 25 points = 14 %
4. > 5 premature ventricular contractions	7	> 26 points = 78 %
5. Age of > 70 years	5	
6. Emergency operations	4	
7. Poor general medical condition	3	
8. Intrathoracic, intraperitoneal, or aortic operation	3	
9. Important valvular aortic stenosis	3	
Detsky Modified Multifactorial Index, 1986[7]		
1. Class 4 angina	20	Cardiac complication rate :
2. Suspected critical aortic stenosis	20	> 15 = high risk
3. Myocardial infarction within 6 mos	10	
4. Alveolar pulmonary edema within 1 week	10	
5. Unstable angina within 3 mos	10	
6. Class 3 angina	10	
7. Emergency operation	10	
8. Myocardial infarction of > 6 mos	5	
9. Alveolar pulmonary edema resolved > 1 week ago	5	
10. Rhythm other than sinus or PACs on ECG	5	
11. > 5 PVCs any time before surgery	5	
12. Poor general medical status	5	
13. Age of > 70 years	5	
Eagle's Criteria For Cardiac Risk Assessment, 1989[8]		
1. Age of > 70 years	1	< 1, no testing
2. Diabetes	1	1 – 2, send for non-invasive test
3. Angina	1	≥ 3, send for angiography
4. Q waves on ECG	1	
5. Ventricular arrhythmias	1	
Lee's Modified Cardiac, 1999[15]		
1. Ischemic heart disease	1	Each increment in points increases risk of post-operative myocardial morbidity
2. Congestive heart failure	1	
3. Cerebral vascular disease	1	
4. High-risk surgery	1	
5. Pre-operative insulin treatment for diabetes	1	
6. Pre-operative creatinine of > 2 mg/dL	1	

ECG : *Electrocardiogram*; PAC : *Pulmonary Artery Catheter*

In managing patients with IHD presenting for non cardiac surgery, initial assessment and planning of the perioperative management is of paramount importance to ensure a smooth anaesthesia and good patient outcome. Planning for perioperative anaesthetic management need to be comprehensive and complete. It starts with patient assessment, stratification of risk and grouping the patients' management according to the risk for anaesthesia and surgery. Intraoperative management include the choice of agents used for induction, maintenance, reversal and analgesic options during and after the operative procedure. Invasiveness of intraoperative monitoring, the plan for reversal and postoperative recovery and subsequent post anaesthesia management need to be decided upon as well as the

level of monitoring and nursing care (e.g. ICU vs HDU vs Ward). It must be done prior to the procedure, involving the relevant personnel that will be administering the anaesthetic, individualised for each patient depending on the patient's assessment and associated medical conditions, surgical procedure and the institutional policies. It needs formal documentation for legal and accreditations use, depending on the policies of the institution.

The aim of this article is to review the literature on the perioperative management of patients with ischaemic heart disease during non-cardiac surgery and formulate a management plan with emphasis on the Malaysian patient population. This article is not meant to substitute the guidelines published by the AHA/ACC,[12] rather it is to be used in concert with the guidelines already published by the relevant organizations.

PREOPERATIVE ASSESSMENT AND RISK STRATIFICATION OF PATIENTS WITH ISCHAEMIC HEART DISEASE PRESENTING FOR NON-CARDIAC SURGERY

The main aim of pre-anaesthetic assessment is to identify patients who are deemed as having a high risk of cardiac morbidity and mortality perioperatively, then to stratify them according to the estimated risk and plan a comprehensive perioperative anaesthetic plan according to the risk group. This is done to reduce the morbidity and mortality plus improve the long term outcome of these patients. To achieve this aim, patients are seen preoperatively either in a pre-anaesthetic assessment clinic (if the institution has one) or in the respective ward when the patient is admitted prior to surgery.

Pre-anaesthetic assessment must be done prior to the surgery and adequate time should be allocated to allow for sufficient assessment, laboratory investigations (if warranted), referrals to the relevant specialities, special investigations (if warranted) and planning for the perioperative anaesthetic management. The assessment preferably should be done by the anaesthetist who will be administering the anaesthetic. However, should it be a policy of the institution, it can be delegated to another qualified personnel who is in direct communication with the anaesthetist who will be managing the patient during surgery.

There were two sets of guidelines published to address the preanaesthetic assessment concerns.[11,12] In 1996, the American College of Cardiology and the American Heart Association published a guideline on the assessment and management of patients going for non-cardiac surgery. The guideline has since been reviewed twice in 2002 and 2007; the latest installment was published in the Journal of the American College of Cardiology (JACC) and Circulation in October 2007.[12] Further discussion will refer to the latter.

The assessment starts with a structured medical history interview and a directed comprehensive physical examination. The aim of the history taking is to determine the presence of active cardiac condition that when present indicate Major Clinical Risk and also the presence of Clinical Risk Factors (according to the Revised Cardiac Risk Index, refer table 2), and the functional status of the patient. Table 3 shows the active cardiac conditions for which the patient should undergo evaluation and treatment before non-cardiac surgery. Table 4 shows the estimated energy requirements for various activities and can be used as a guide to assess the functional status of a patient during the pre-anaesthetic visit. A directed physical examination is done to elicit signs associated with the above (please refer Table 3). Laboratory investigations are done according to the medical status as found in the history and physical examination.

TABLE 3 : Active cardiac condition for which the patient should undergo evaluation and treatment before non-cardiac surgery

CONDITION	EXAMPLES
Unstable Coronary Syndromes	Unstable or severe angina* (CCS class III or IV)† Recent MI¥
Decompensated HF (NYHA functional class IV; Worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block Mobitz II atrioventricular block Third-degree atrioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR greater than 100 bpm at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Severe Valvular Disease	Severe aortic stenosis (mean pressure gradient greater than 40 mm Hg, aortic valve area less than 1.0 cm^2, or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

CCS : *Canadian Cardiovascular Society*; HF : *Heart Failure*; HR : *Heart Rate*; MI : *Myocardial Infarction*; NYHA : *New York Heart Association*.

*According to Campeau[10]

†May include "stable" angina in patients who are unusually sedentary

¥The American College of Cardiology National Database Library defines recent MI as more than 7 days but less than or equal to 1 month (within 30 days)

TABLE 4 : The estimated energy requirements for various activities

	Can you…		Can you…
1 MET	Take Care Yourself?	4 METs	Climb a flight of stairs or walk up a hill?
↓	Eat, dress or use the toilet?	↓	Walk on level ground at 4 mph (6.4 kph)?
↓	Walk indoors around the house?	↓	Run a Short distance?
↓	Walk a block or 2 on level ground at 2 to 3 mph (3.2 to 4.8 kph)?	↓	Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
4 METs	Do light work around the house like dusting or washing dishes?	↓	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
		Greater than 10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

kph : *Kilometers Per Hour*; MET : *Metabolic Equivalent*; mph : *Miles Per Hour*

*Modified from Hlatky et al[11], copyright 1989, with permission from Elsevier, and adapted from Fletcher et al[12]

The ACC/AHA guideline advocates the use of a stepwise approach for perioperative cardiac assessment.[12] Figure 1 shows the algorithm for cardiac evaluation and care for non cardiac surgery. The algorithm used has been modified to incorporate findings from recent random controlled trials and cohort studies. The ACC/AHA guideline also give recommendations for assessment of specific diseases and surgical procedures, supplemental preoperative evaluation, perioperative interventional and medical therapy, anaesthetic considerations, intraoperative management, perioperative surveillance, postoperative and long term management.[12] Table 5 summarises the recommendations for perioperative beta-blocker therapy.

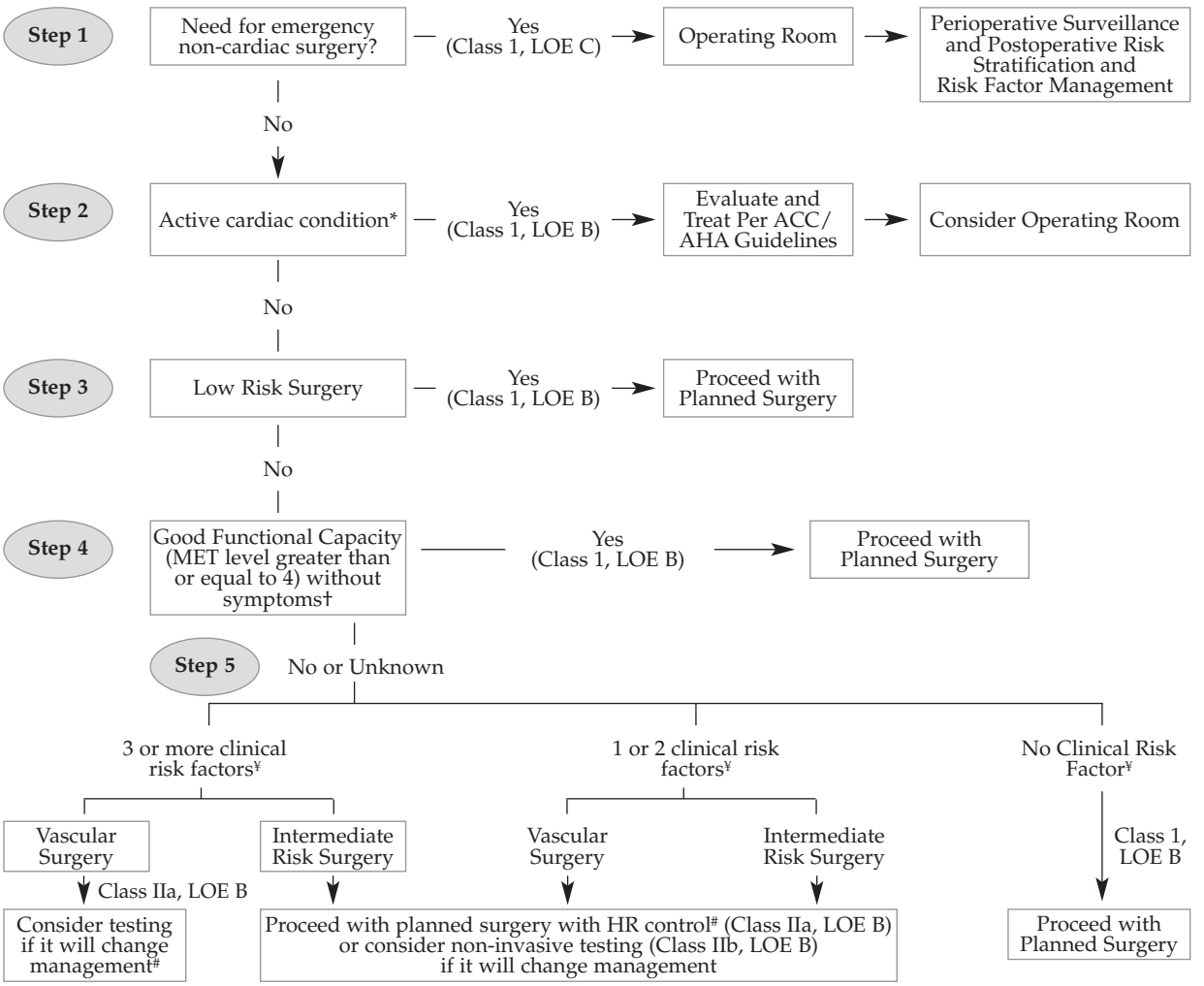

FIGURE 1 : Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or greater. *See Table 3 for active clinical conditions. †See Table 4 for estimated MET level equivalent. ¥Clinical risk factors include ischemic heart disease, compensated or prior HF, diabetes mellitus, renal insufficiency, and cerebrovascular disease. #Consider perioperative beta blockade (see Table 5) for populations in which this has been shown to reduce cardiac morbidity/mortality.

ACC/AHA : *American College of Cardiology/American Heart Association*; HR : *Heart Rate*; LOE : *Level of Evidence*; MET : *Metabolic Equivalent*.[12]

TABLE 5 : Recommendations for perioperative beta-blocker therapy based on published randomized controlled trials

Surgery	No Clinical Risk Factors	1 or More Clinical Risk Factors	CHD or High Cardiac Risk	Patients Currently Taking Beta Blockers
Vascular	Class IIb, Level of Evidence : B	Class IIa, Level of Evidence : B	Patients found to have myocardial ischemia on pre-operative testing : Class I, Level of Evidence : B*	Class I, Level of Evidence : B
			Patients without ischemia or no previous test : Class IIa, Level of Evidence : B	
Intermediate Risk	…	Class IIb, Level of Evidence : C	Class IIa, Level of Evidence : B	Class I, Level of Evidence : C
Low Risk	…	…	…	Class I, Level of Evidence : C

See **TABLE 6** for definition of procedure. Ellipses ( ) indicate that data were insufficient to determine a class of recommendation or level of evidence. See text for further discussion.

CHD : *Coronary Heart Disease*.

*Applies to patients found to have coronary ischemia on pre-operative testing.
†Applies to patients found to have coronary heart disease.

TABLE 6 : Cardiac Risk* Stratification for Noncardiac Surgical Procedures

Risk Stratification	Procedure Examples
Vascular (reported cardiac risk often more than 5 %)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1 % to 5 %)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopaedic surgery Prostate surgery
Low† (reported cardiac risk generally less than 1 %)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and non-fatal myocardial infarction.
†These procedures do not generally require further preoperative cardiac testing.

MEDICAL THERAPY BEFORE SURGERY

There are few randomized trials involving medical therapy before non cardiac surgery to prevent cardiac complications and most look at surrogate end points of ischaemia evidenced by ECG changes and lack the power to address myocardial infarction or cardiac death.[12]

Mangano randomly assigned high risk patients to receive either atenolol or placebo for seven days prior to surgery. There was no difference in perioperative mortality but the atenolol group had a significantly improved six month survival rate.[14]

CHOICE OF ANAESTHETIC TECHNIQUE

There appears to be no best myocardium protective anaesthetic technique. The choice of anaesthetic technique and the use of intraoperative monitoring equipment depend on the integration of patient and surgery specific factors.[15,16]

All anaesthetic techniques must aim to keep myocardial oxygen supply greater than demand and therefore avoid myocardial ischaemia. The essential requirements in patients with ischaemic heart disease are to avoid tachycardia and extremes of blood pressure which adversely affect myocardial oxygen supply and demand.[17]

CONDUCT OF ANAESTHESIA

Premedication is essential as a nervous patient is prone to be tachycardic and hypertensive and this is not desirable in the patient with ischaemic heart disease. Beta blockers and an anxiolytic are usually helpful in preventing unwanted haemodynamic effects which can provoke myocardial ischaemia.[17]

Most intravenous induction agents have a direct depressant action on the myocardium and reduce vascular tone but etomidate and benzodiazepines may be less problematic in this regard. Hypotension may occur and may cause a resultant tachycardia and this is usually more pronounced in a hypovolaemic patient which is frequently seen as a result of prolonged fasting.[18] Ketamine is unique as it causes indirect stimulation of the symphathetic system and causes tachycardia and hypertension.[18]

There appears to be no one superior inhalational agent for the maintenance phase of anaesthesia in the patient with ischaemic heart disease.

Isoflurane historically was avoided due to fears of coronary steal syndrome but data accumulated from large scale human studies have disproved it. Sevoflurane has been used favorably in high risk non cardiac surgery patients with no increase of myocardial ischaemia noted. Desflurane which may cause tachycardia was shown to have significantly higher rate of myocardial ischaemia as opposed to a narcotic based technique but no increase in the rates of myocardial infarctions.[19]

Adequate pain relief is of paramount importance and high dose narcotics reduce the stress response to surgery with minimal myocardial depression. However this form of analgesia has the disadvantage of respiratory depression necessitating postoperative ventilation. The emergence of newer rapid acting narcotics such as remifentanil may eliminate this problem.[20]

REGIONAL ANAESTHESIA

Epidural anaesthesia has haemodynamic advantages by reducing both preload and afterload. It also has beneficial effects on the coagulation cascade and excellent postoperative pain relief may be attained by using an infusion of local anaesthetic and opiate.[21] However failure to provide adequate block should be avoided as this will lead to an increase in the stress response and may give rise to myocardial ischaemia.[22] Another factor that has to be considered is that some patients with ischaemic heart disease may have had a drug eluting stent placed during treatment of their coronary disease. There is controversy with regards to the duration of dual anti platelet therapy needed to prevent in-stent stenosis. Hence regional anaesthesia may be contraindicated in some of these patients.[12]

POSTOPERATIVE PAIN MANAGEMENT

Patient controlled intravenous or epidural analgesia is a popular method of reducing postoperative pain. Several studies suggest that effective pain management leads to reduction in postoperative cathecholamine surges and hypercoagulabilty.[23]

GENERAL CONSIDERATIONS FOR PATIENTS WITH IHD

There is insufficient data to support the prophylactic use of intravenous nitoglycerine in the high risk patient for coronary artery disease. Furthermore anaesthetic agents may mimic the action of nitroglycerine on preload and afterload and cause

significant hypotension and myocardial ischaemia. The use of nitroglycerine patch or paste should be avoided as its absorption is erratic. Current AHA/ACC guidelines indicate nitroglycerine as a Class 1 indication for patients previously taking nitroglycerine who have active signs of myocardial ischaemia without hypotension.

Another important consideration that needs to be looked at is body temperature as patients that maintained normothermia demonstrated a reduction of perioperative cardiac events. Hypothermia was associated with an increased risk of myocardial ischaemia in patients with a core body temperature of less than 35.5 degrees Celsius.[24]

Patients who have proven ischemic heart disease may not tolerate anaemia well but data from multicentre trials is lacking. A small retrospective trial in which patients with a haematocrit of less than 27% undergoing infra inguinal bypass had higher rates of myocardial infarction.[25]

PERIOPERATIVE MONITORING

The use of ST segment analysis from the electrocardiogram (ECG) in appropriately selected patients at high risk may improve the sensitivity for detection of myocardial ischaemia. Leads II and V5 are able to detect 80% of all ischaemic changes detected in a 12 lead ECG. Intraoperative and postoperative ST segment changes indicating myocardial ischaemia are strong predictors of perioperative myocardial infarction in the high risk patient undergoing non cardiac surgery. Conversely, ST depression in the low risk patient is often not associated with regional wall motion abnormalities.[12]

The routine use of pulmonary artery catheters (PAC) is not supported by current data. Randomized trials using PAC versus central venous catheters in abdominal aortic surgery and major vascular surgery show no difference in end points of myocardial infarction and cardiac death. The American Society of Anaesthesiologists (ASA) guidelines on placement of PAC hinges on three factors;

1. Severity of disease
2. Magnitude of anticipated surgery
3. Practice setting

Patients who are most likely to benefit are those with recent myocardial infarction complicated by heart failure, surgical procedures in which intra and postoperative fluid shifts are a dominant factor. Practice settings in which interpretation of data derived from PAC is used for optimal benefit.[26]

Transesophageal Echocardiography (TEE) has been documented to be more sensitive in detecting myocardial ischaemia compared to ST segment analysis on the ECG and data obtained from PAC. However TEE is a poor predictor of cardiac morbidity in the non cardiac surgery patient. Hence the routine use of TEE in the non cardiac surgery patient is not warranted.[27]

The use of Intra-Aortic Balloon Pump (IABP) has been suggested as a means of reducing perioperative cardiac risk in the non cardiac surgery patient. Several case reports have documented its use in patients with unstable coronary syndrome or severe coronary artery disease undergoing urgent non cardiac surgery. IABP usage is associated with limb ischaemia especially in patients with vascular insufficiency and there is no evidence to support its routine use at this juncture.[28]

POSTOPERATIVE CARE

Depending on the patient's condition and the nature of surgery performed, the patient may need to be admitted to the Intensive Care Unit (ICU) or High Dependency Unit (HDU).[29] Particular attention should be placed on ensuring optimal heart rate, haemodynamics and blood loss from surgical drainage. The need to ensure adequate pain relief and prevention of hypoxia cannot be overemphasized.

SURVEILLANCE FOR PERIOPERATIVE MYOCARDIAL INFARCTION

The optimal method of diagnosing perioperative myocardial infarction has been the focus of several studies looking at perioperative myocardial infarction in the non cardiac surgery patient. Among the strategies used have been clinical symptoms, postoperative ECG changes and elevation of

biochemical markers (Creatinine Kinase-MB, troponin I and troponin T). In the high risk patient, ECG obtained at base-line, immediately after surgery and two hours after surgery appear to be reliable and cost effective.[12]

CONCLUSION

Achieving a successful outcome in the patient with coronary artery disease undergoing non cardiac surgery requires teamwork and communication between surgeon, cardiologist and anaesthesiologist. The use of both invasive and non invasive preoperative testing should be limited to those tests that will have an impact on patient management. Lastly, non cardiac surgery may be the first opportunity a patient receives appropriate assessment. Risk modification modalities should be instituted at this juncture to ensure cardiac longevity.

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Anaesthesia For The Severely Premature And Extremely Low Birth Weight Infants

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DEFINITIONS

Premature infants are defined as neonates with a gestational age of less than 37 weeks, and severely premature infants are those born after less than 28 weeks of gestation.

Low birth weight (LWB) infants are defined as infants born with a birth weight of less than 2500 grams, very low birth weight (VLBW) infants are those with a birth weight of less than 1500 grams and extremely low birth weight (ELBW) are infants with birth weight of less 1000 grams.

INTRODUCTION

The survival rate of the severely premature and extremely low birth weight (ELBW) babies has increased dramatically over the last 20 years.[1] In the United States[1] and Australia,[2] survival at 23 weeks of gestation is 20-25% with some centres reporting survival as high as 41-48%. With this increased survival rate, the opportunities for these babies to undergo surgery are increasing. This has a wide implication for neonatal anaesthesia.

PROBLEMS PECULIAR TO SEVERELY PREMATURE AND VLBW INFANTS

There are problems that are peculiar and exclusive to the severely premature and very low weight infants. Most of the important organs in these babies are still in the process of development and maturation. There is inadequate production of efficient surfactant, a susceptibility of retinal blood vessels to oxygen toxicity and a susceptibility to haemorrhagic and ischaemic brain damage. These lead to the development of disease exclusively found in these babies e.g. respiratory distress syndrome, intraventricular haemorrhage, retinopathy of prematurity, patent ductus arteriosus and necrotizing enterocolitis. Other problems include hypoglycaemia, apnoea especially during post-operative period and hypothermia.

Respiratory Distress Syndrome

Preterm babies of less than 32 weeks gestation are more at risk of developing respiratory distress syndrome. It is characterized by increasing atelectasis over the first few days after birth secondary to inadequate production of surfactant. The preterm lung has less surfactant than term lung and the surfactant is intrinsically defective. It has a low protein/lipid ratio and is less effective in improving lung compliance.

The introduction of artificial surfactant replacement therapy in the late 1980s has dramatically improved the prognosis of these infants

Apnoea

Apnoea is usually defined as absent respiratory airflow for 20 seconds or longer. Prolonged apnoea is accompanied by hypoxia, hypercarbia and bradycardia. Hypothermia, hypoglycaemia and anaemia are known inducing factors of apnoea. Apnoeic spells are also frequently observed in preterm infants and ex-preterm infants during recovery from general anaesthesia.

Brain Injury

Brain injury, in the premature infants, include intraventricular haemorrhage, cerebral ischaemia (periventricular leukomalacia) and posthaemorrhagic hydrocephalus.

Intraventricular haemorrhage (IVH) is the most common cause of intracranial haemorrhage in VLBW infants. The incidence and severity of IVH is directly correlated with the degree of prematurity. Hypoxia, hypercapnia, hypoglycaemia and anaemia are associated with a rise in cerebral blood flow which may induce the onset of IVH. The outcome for infants with IVH depends, to a large extent, on the degree of associated parenchymal injury.

Periventricular leukomalacia is due to impairment of blood supply to cerebral white matter. Severe hypotension, marked hypocarbia, and impairment of cerebral autoregulation in these infants are some of the risk factors leading to insufficient cerebral blood flow and ischaemia.

Retinopathy of Prematurity (ROP)

The pathophysiology of ROP is thought to be due to retinal artery constriction leading to retinal ischaemia resulting in neovascularization. Known risk factors are prematurity and low birth weight. Its severity is inversely proportional to birth weight and gestational age.[3,4] Other contributing factors include use of supplemental oxygen, fluctuation in oxygen saturation, mechanical ventilation, total parenteral nutrition and blood transfusion.[5]

Thermogenesis

Premature and LBW infants are susceptible to hypothermia during surgery. Neonates depend on nonshivering thermogenesis for heat production Non-shivering thermogenesis utilises brown adipose tissue and requires oxygen consumption. It is believed that in small premature infants brown adipose tissue are not sufficiently developed and combined with the thin skin and the larger surface/volume ratio, they are more susceptible to hypothermia.

Volatile anaesthetics are potent inhibitors of brown adipose tissue thermogenesis[6,7] while nitrous oxide and intravenous anaesthetics such as thiopental and propofol do not have this inhibitory property.[8] General anaesthesia using volatile anaesthetics places LBW infants at higher risk for hypothermia.

Necrotising Enterocolitis

Necrotising enterocolitis (NEC) is more common in premature than in term newborns. LBW is the most important risk factor for NEC. The prognosis for ELBW infants with NEC is poor, with a mortality rate greater than 30%.[9]

Although the pathogenesis of NEC has not been fully established, 3 main contributors have been implicated in the development of NEC. They are hypoperfusion of the gut due to systemic hypoxia or hypotension, infection and enteric feeding. Other factors include exposure to antenatal glucocorticoids, vaginal delivery, the need for mechanical ventilator support, patent ductus arteriosus (PDA), exposure to postnatal indomethacin and a low Apgar score at 5 minutes.[10]

The classical picture is a triad of symptoms: abdominal distension, bile-stained vomiting, and bloody frothy stool. There may be signs of systemic sepsis – circulatory collapse, hypotension, apnoea and occasionally signs of gut perforation. Thrombocytopenia commonly occurs and may require correction. Initial management includes resuscitation, cardiopulmonary support and antibiotics. Large volumes of colloids may be required together with blood and blood components. Surgical intervention may be required when there is perforation, and when there is continuing deterioration despite full support.

Hypoglycaemia

Premature and low birth weight infants are susceptible to hypoglycaemia. This is attributed to immature gluconeogenic and glycogenolytic enzyme systems. A plasma glucose concentration of less than 25 mg/dl in these infants is taken as hypoglycaemia. Infants who utilise glucose at an increased rate are prone to hypoglycaemia e.g. infants experiencing perinatal asphyxia, in neonatal sepsis and a cold environment.[11]

Glucose levels in infants at increased risk of hypoglycaemia should be checked intra operatively. Intravenous infusions should contain glucose and to maintain a glucose infusion rate of between 6-8 mg/kg/min.

PAIN SENSATION

There is increasing evidence that pain pathway in low birth weight infants is fully active and they are sensitive to pain and stress. Inadequate anaesthesia and analgesia result in massive stress response that can hinder post-op recovery. Hence the appropriate use of analgesics and sedatives are indicated for surgery and painful procedures.

PHARMACOKINETICS AND PHARMACODYNAMICS OF DRUGS

The pharmacokinetics and pharmacodynamics of drugs in premature and low birth weight infants are different from that of the term babies, children or adults. Immaturity of the liver, kidneys and receptors result in handling of drugs in a less predictable fashion.

Main factors affecting drug pharmacokinetics in very premature/low birth weight infants are higher body water than fat content resulting in higher volume of distribution, hence a need for a higher loading dose and a decrease in albumin and α1 acid glycoprotein binding leading to increase in free drug concentration. Biotransformation of drugs by hepatic enzyme systems may be slower due to immaturity of the system. Renal excretion of drugs may be slow or impaired due to low renal blood flow, low glomerular filtration rate and poor tubular secretion.

The minimal alveolar concentration (MAC) of inhalational anaesthetics is lower in preterm infants compared with that in full term neonates and older infants. Isoflurane is the only inhalational anaesthetic whose MAC has been measured in preterm infants.[12]

As a result of this altered pharmacokinetics and pharmacodynamics, drugs must be used with care in these infants, and their clinical effects should be monitored frequently. To avoid toxicity drugs should be given in smaller doses with longer intervals.

PERIOPERATIVE CARE OF SEVERELY PREMATURE AND VLBW INFANTS

The most frequent diseases for which surgery is required in VLBW infants are ROP, PDA, NEC, ventriculo-peritoneal shunt and inguinal hernia. They may be seriously ill and superimposed with prematurity-related disease. Precautions should be taken in order to deliver a safe anaesthesia to these infants.

Choice of Operation Site

There is much discussion as to the best place to perform surgery in severely premature and VLBW infants - operating theatre or neonatal intensive care unit.

Anaesthesiologists and surgeons are more comfortable performing surgery in an operating theatre which allows them to work in a familiar place with access to the assistance of colleagues and nursing staff, and a variety of surgical or anaesthetic equipment. Operative conditions are more sanitary in the operating theatre. On the other hand, performing surgery in the neonatal intensive care unit avoids transportation of the patient which may be accompanied by a significant amount of risk. In order to transport the sick patient under similar conditions to those in the neonatal intensive care unit, an incubator, ventilator, monitors, oxygen and air cylinders and many volumetric syringe pumps must be carried together while maintaining the same ventilatory and inotropic support.

There is clearly no answer as to which is the best site. The decision should be made based on the setting and conditions in each individual case and institution.

Transport

Transport of sick and small infants requires experienced staff and appropriate equipment. They should be transported from the ward to the operating theatre and vice versa in a warm and humidified incubator. A seriously ill patient may have to be transported under similar conditions to those in NICU, maintaining similar ventilatory and inotropic support.

Induction of Anaesthesia

Anaesthesia may be induced using either an inhalational agent or an intravenous agent. Ketamine (1.5–2 mg/kg) can be used in hemodynamically compromised patients. Often patients come with endotracheal tube in place from NICU. If the endotracheal tube is not in place, endotracheal intubation should be performed after induction of anaesthesia except for rare cases of moribund patients. Endotracheal intubation can be performed under deep volatile agent or with muscle relaxant. Endotracheal intubation without anaesthesia or sedation may cause an acute rise in arterial and intracranial pressure, leading to IVH. Intravenous atropine 0.01mg/kg may be given prior to intubation to counter bradycardia which can occur during intubation. The position of the tracheal tube should be carefully confirmed to avoid endobronchial intubation.

Maintenance of Anaesthesia

Anaesthesia can be maintained with air-oxygen mixture combined with a volatile agent, muscle relaxant and fentanyl. Sevoflurane or isoflurane can cause cardiodepression when used in higher doses. Nitrous oxide is not suitable for the anaesthesia in VLBW infants, since the FiO_2 should be titrated with air and oxygen to maintain the PaO_2 and SpO_2 at the most suitable value for the patient. It should be avoided in abdominal surgery because it tends to distend the intestines. Haemodynamic state should be maintained in as stable a level as possible to avoid an abrupt increase or decrease in cerebral blood flow, which may lead to intracerebral haemorrhage or cerebral ischaemia. Hypoxia, hypercapnia, hypoglycaemia and anaemia are all associated with a rise in cerebral blood flow, predisposing the infant to the development of intracerebral haemorrhage and, inversely, hyperoxia and hypocapnia are associated with a decrease in cerebral blood flow, predisposing to cerebral ischaemia. It is important to avoid hyperoxia as it is associated with development of ROP. FiO_2 should be kept as low as possible, including during transport to avoid exposure to high level of oxygen. SpO_2 should be kept in the range of 90-95%.

Premature and low birth weight infants should be placed in a warm environment using various warming devices during transport and surgery. Appropriate warming devices include warm operating room, a warming mattress and a forced-air warming system. Keeping the infant's head covered and skin and drapes dry are also important.

Intra-Operative Monitoring

Basic monitoring include electrocardiogram, blood pressure, pulse oximetry, end-tidal carbon dioxide and temperature. For major surgery, invasive blood pressure monitoring, central venous pressure and urine output may be needed. Intraarterial cannula may be sited at umbilical artery, radial artery or posterior tibial artery.

Regional Anaesthesia

There is increasing evidence that regional anaesthesia is beneficial when used alone or in combination with general anaesthesia in VLBW infants. Epidural anaesthesia has been shown to decrease the need for postoperative ventilatory support in neonates undergoing major surgery.[13] Huang and Hirshberg[14] showed that regional anaesthesia decreased the need for postoperative mechanical ventilation in infants with a mean gestational age of 26 weeks and a mean postconceptual age at surgery of 38 weeks, when undergoing herniorrhaphy. Good success rate and low complication rates have also been reported.[15]

Emergence From Anaesthesia

Extremely premature and VLBW infants who were mechanically ventilated before surgery should remain ventilated during the return journey to NICU.

The trachea need not be extubated in the operating room immediately after the surgical procedure even if the infant was not on a ventilator before surgery. The trachea can be extubated later in NICU when full recovery from the remaining effects of the anaesthetic is obtained.

Post-Op Management

Preterm infants tend to have apnoeic spells postoperatively. The generally accepted limit of such a risk in neonates is 44–46 weeks postconceptual age.

Monitors should be applied to detect apnoea, desaturation and bradycardia in these infants for at least 48 hours postoperatively.

CONCLUSION

The severely premature and very low birth weight infants present significant challenges to the anaesthesiologist. They are susceptible to prematurity-related diseases. When providing anaesthesia for these infants, precautions should be taken in order to deliver a safe anaesthesia. Attention should be paid to the inspired oxygen concentration to avoid hyperoxia which is a major contributing factor to the development of retinopathy of prematurity. Haemodynamic parameters should be kept stable in order to avoid intraventricular haemorrhage and cerebral ischaemia. Prevention of hypothermia and hypoglycaemia is also essential. These infants handle drugs in less predictable fashion, and therefore there is a need to titrate drug dosages. They will benefit from adequate anaesthesia and analgesia.

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Special Anaesthetic Considerations For Syndromic Children

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INTRODUCTION

Syndromes are groups of anomalies which usually contain certain malformations or sequences. These malformations can range from simple deformity of the limbs or craniofacial structures to severe cardiac abnormality which may lead to incompatibility to life. However, due to various degrees of genetic transmission and penetrance, the expressions of these malformations or its phenotype in certain syndromes may also be variable.[1] Moreover, some sequences are pathognomonic to the syndrome whereas others may just be totally absent in individuals with that syndrome.

Therefore, the diagnosis of syndromic children is not solely dependent on the recognition of certain manifestations of the anomalies but rather a culmination of careful history-taking, physical examination and / or chromosomal studies.[2]

Although congenital syndromes are relatively rare (ranging from 1/600-800 births in Down's Syndrome to 1/20,000 births in mosaicism or trisomy 8), the numbers of these children surviving beyond their normal life expectancy are in a rising trend owing to the advent of modern medicine. This has indirectly led to an increased frequency of presentation of these syndromic children to the anaesthesiologist for various surgical or non-surgical procedures. These procedures, be they diagnostic or therapeutic in nature, may involve various disciplines namely general surgery, cardiothoracic, plastic & reconstructive, orthopaedic, neurosurgery, otorhinolaryngology, ophthalmology, dental surgery, radiology, intensive care as well as emergency medicine .

Provision of anaesthesia to these groups of children is indeed most daunting for the anaesthesiologist owing to several reasons in particular concerning the recognition of the anomalies, co-existing medical/ surgical problems and avoidance of notorious anaesthetic complications associated with certain syndromes.[3]

Hence, successful peri-operative management for these children depends substantially on comprehensive planning by the attending anaesthesiologist, which includes careful pre-operative evaluation with close collaboration among colleagues from various disciplines, meticulous intra-operative monitoring and anticipation of difficulties or complications that may arise as well as possible post-operative intensive care management.

GENERAL CONSIDERATIONS

Paediatric patients have markedly different physiological and structural aspects in comparison to the adults; hence the conduct of paediatric anaesthesia poses several unique considerations. The level of difficulty whilst managing these patients is dependent on their weight, size, maturity, type and duration of procedures, the functional status of the patient's organ systems as well as the presence and nature of certain syndromes.

The common issues of concern which the anaesthesiologist needs to address include the following:

1. Difficulty in obtaining vascular access[4]
2. Hypothermia due to greater radiant heat loss and poor thermogenesis particularly during prolonged surgery[5]
3. Relatively small intravascular volume with lower tolerance to blood loss[6]
4. In cases of difficult airway, there is limited options of difficult airway management devices especially among very small babies

5. Possible post-operative apnoea especially for those with gestational age less than 50 weeks
6. Frequent upper respiratory tract infections with hyperactive airway reflexes and associated bronchospasm or laryngospasm
7. Altered pharmacokinetics and pharmacodynamic of drugs, in particular anaesthetic agents.

SPECIAL CONSIDERATIONS

Difficult Airway

Apart from the above-mentioned common peri-operative problems faced during provision of paediatric anaesthesia, syndromic children also present specific problems which are unique to their condition. The anaesthesiologist must be well equipped with not only intimate knowledge of the normal anatomy of the paediatric airway but also awareness of the possible malformations found in various congenital disorders or syndromes.[7] For instance, the presence of dysmorphic facies among the *Apert*, *Crouzon* (craniofacial dystoses), *Goldenhar* (under-developed mandible), *Pierre-Robin* and *Treacher Collin* (severe micrognathia) may render mask-holding and manual ventilation difficult during induction of anaesthesia. Furthermore, some of these craniofacial deformities may distort and produce "out-of-axis" laryngoscopic views hence rendering trachea intubation incredulously difficult.

The presence of cervical vertebral laxity as found in *Marfan's*, *Down's* or *Trisomy 21* and *Ehlers-Danlos* can lead to possible cervical vertebral displacement and cord injury during the act of endotracheal intubation. On the other hand, the presence of cervical vertebral fusion, atlanto-occipital abnormalities and spinal canal stenosis in *Klippel-Feil* can cause limited neck mobility and isolated difficult intubation without problems in mask ventilation.[8]

In addition, some difficult airways are progressive in nature as demonstrated in children afflicted with *mucopolysaccharidoses disease* which is a group of inherited storage disease caused by deficiency of lysosomal enzymes that degrade glycosaminoglycans (GAGs), also known as mucopolysaccharides.[7] In this group of children, the deficiency in carbohydrate enzymatic metabolism pathway leads to deposition of GAGs at various parts of the body. In particular, infiltration of GAGs into the upper airway tract causes progressive enlargement of the tongue and thickening of oropharyngeal structures which may eventually lead to upper airway obstruction with increasing difficulty in mask ventilation and intubation as these children grow older. This condition is prevalent in children afflicted with syndromes like *Hurler*, *Sly* and *Sanfilippo type A* to *C*.

In addition, the presence of limited opening to the upper airway passage such as in *Freeman-Sheldon (Whistling-Face)* with small and contracted mouth may render the endotracheal intubation by direct laryngoscopy almost impossible.[9]

Unfortunately, the identification of children with potential airway difficulty is not always easy and is often discovered only during induction of anaesthesia which is most distressing for the patient as well as for the anaesthesiologist. As such, the "difficult airway cart" with its repertoire of face masks, endotracheal tubes and various airway adjuncts (namely bougie, laryngeal mask airway, nasopharyngeal airway and/or tracheostomy kit) should be made easily accessible at all times, in particular while conducting anaesthesia for emergency cases.

Other issues of concern include the possible difficulty in achieving a good anchor of endotracheal tube owing to the patient's abnormal facial structure, unusual positioning of patient for surgery and a shared airway with the surgeon as found in repairs of cleft lip/palate which are common occurrences among syndromic children. As such, appropriate intra-operative monitoring in particular continuous capnography and pulse oximetry monitoring should be made mandatory irregardless of the simplicity and duration of the procedure.

Mental Challenge

While normal paediatric patients are already difficult to manage in the operating theatre setting in view of their constant attention needs and apprehension in a strange environment, management of syndromic children is even more challenging. This is attributed to the fact that syndromic children are at a higher propensity of being mentally challenged. Certain genetic syndromes such as the *Down's* and *Fragile X's*

contribute up to 21% of the total number of children with severe mental retardation (MR).[10] These children are often uncooperative and restless when they arrive at the operating complex and may occasionally require sedation. The anaesthesiologist should contemplate the risks and benefits of preoperative sedation carefully before embarking on it as these children are at higher risk of respiratory embarrassment secondary to their pre-existing upper airway pathology. Hence, the need for sedation among syndromic children must be individualized. On the other hand, parental presence during induction of anaesthesia should be encouraged especially for those more than 6 months of age (usual age when the children attain stranger anxiety) as this measure is often proven successful in alleviating an uncooperative child's anxiety.

Increased Intra-Cranial Pressure

The administration of anaesthetic agents, in particular inhalational agents may alter the secretion as well as the adsorption of cerebrospinal fluid.[11] This is of particular importance for those children with an inherently elevated intra-cranial pressure (ICP) such as those with severe craniofacial deformities and congenital hydrocephalus. Any precipitous surge in ICP in these patients during the peri-operative period could lead to a detrimental outcome. The patency and proper functioning of ventriculo-peritoneal shunt if present should be ensured preoperatively. The altered pharmacokinetics of anti-convulsant agents in the face of altered physiology in these patients should be taken into consideration also as they may require dosage adjustments to ensure adequate seizure control.[11,12] Hence, determination of drug blood levels via laboratory measurements during peri-operative period is indeed most helpful.

Unfortunately, some of these children may have already developed manifestations secondary to longstanding elevated ICP. Often, the presence of altered sensorium, compromised swallowing reflexes and lack of protective airway reflexes would easily lead to higher risk of upper airway obstruction, gastric content aspiration and apnoea during the post-operative period. As such, provision of anaesthesia for these patients should not only be targeted towards preservation of the ICP but also measures to ameliorate the compromised consciousness level, upper airway patency, possibility of aspiration as well as post-operative apnoea.

Cardiovascular Disorders

The incidence of congenital heart defects (CHD) approximate 0.8% of live births. These occurrences are more common in syndromic children. These abnormalities can range from simple septal defects to life-threatening major structural abnormalities. Basically, these defects can be meaningfully characterized into the following:

1. Increased pulmonary blood flow lesions like atrial or ventricular septal defects and patent ductus arteriosus
2. Decreased pulmonary blood flow lesions such as Tetralogy of Fallot, pulmonary atresia, tricuspid atresia, Ebstein anomaly, transposition of great arteries and truncus arteriosus
3. Obstructive lesions with pressure overload such as coarctation of aorta, pulmonary stenosis and aortic stenosis

Furthermore, some syndromes are known to have associated cardiac conduction abnormalities. Examples are the association between *Romano-Ward* with long QT syndrome and malignant tachyarrhythmias as well as *Brugada* with cardiac arrest and sudden death.[13]

Again, a multi-disciplinary approach is prudent with aims at minimizing morbidity and mortality to these children. Hence, whenever congenital heart disease is suspected, cardiology evaluation is warranted so that a thorough examination along with cardiac functional status evaluation and optimization can be carried out prior to surgery. Transthoracic echocardiography remains one of the investigator's tools of choice for its non-invasive nature and ability to provide information such as identification of defect types, presence of intra-cardiac shunt or obstructive lesions and detection of secondary complications such as intra-cardiac micro-organism vegetation, abnormal myocardial wall motion, reversal of shunt etc.

Generally, the choice of drugs is not as important as an understanding of the pathophysiology of the lesion. The anaesthesiologist would need to consider

the development of haemodynamic goals for each patient in terms of heart rate, contractility, preload, afterload, systemic vascular resistance and pulmonary vascular resistance. Many anaesthetic agents can be used so long as they are administered in a thoughtful fashion.

Nil per orally guidelines used for other infants and children generally can be used for patients with CHD, though in addition meticulous care should be given to the state of hydration in a child with cyanotic heart disease. If uncertainty exists concerning the precise time of surgery, intravenous fluid infusion is indicated to prevent dehydration especially in the presence of polycythaemia and hyperviscosity as well as to ensure adequate intra-vascular volume in these patients.[14]

Other considerations would include antibiotics for endocarditis prophylaxis for patients undergoing invasive procedures, meticulous care to avoidance of air bubbles within the parenteral injection parts, anticipation and management of interaction of anaesthetic agents with cardiac medications such as digoxin, aspirin, anti-failure medications, anticoagulants and so forth.

Respiratory Disorders

Concomitant respiratory disorders among syndromic children are common. The defects can be either structural (like bronchopulmonary hypoplasia and restrictive effect secondary to severe scoliokyphosis) or functional in nature (such as shunt and dead-space ventilation). Of note, syndromes which are associated with choanal stenosis or atresia will render children with craniofacial dysostosis becoming fastidious mouth breathers. In such cases, the anaesthesiologist should ensure patent oral airway (either maintaining mouth-opening or inserting oropharyngeal airway) while mask ventilating these group of patients.

On the other hand, musculoskeletal diseases like *Duchenne muscular dystrophy*, *Apert's* and *Noonan's* are prone to respiratory distress due to respiratory muscle insufficiency. Moreover, these children are sensitive to neuromuscular junction blockade agents (NMBA) and require careful NMBA titration and close musculoskeletal function monitoring during anaesthesia.

Mitochondrial Cytopathies

Mitochondrial cytopathies (MC, mitochondrial myopathies or inherited mitochondrial encephalomyopathy) are genetic disorders which are associated with various syndromes such as *Myoclonic Epilepsy with Ragged Red Fibers* [MERRF syndrome],[15] *Mitochondrial Encephalomyopathy*, *Lactic Acidosis* and *Stroke-like* [MELAS syndrome] and *Neuropathy*, *Ataxia*, *Retinitis Pigmentosa* [NARP syndrome]. The mutations result in defective mitochondrial oxidative phosphorylation within the mitochondria and consequently jeopardize cellular bio-energy generation. This in turn leads to an impaired cellular ability to withstand oxidative stresses such as mechanical insults, infection, hypoxia, toxin or drugs administration. In the face of prolonged adverse events, apoptosis or cell death will follow suit.[16]

Clinically, these patients present with hypotonia and muscle weakness upon exposure to such triggering factors. The inherent defective neuronal bioenergetics mechanism of central nervous system (encephalomyopathy) may enhance the depressive effects of anaesthetic agents. These patients yield myasthenia-like effects following administration of anaesthetic agents in the operating theatre. The resultant bulbar and respiratory muscle weakness may give rise to hypoventilation as well as gastric content aspiration in the immediate post-operative period. On the other hand, intra-operative blood sugar and lactate level monitoring are important in order to ensure adequate bio-energy generation. Besides, if general anaesthesia is unavoidable, tracheal intubation with intermittent positive pressure ventilation (IPPV) is a more feasible option compared to spontaneous respiration to avoid unnecessary metabolic exhaustion, ensure adequate oxygenation and avoidance of hypoxia.

The defective myocardial bioenergetics mechanism may also result in an increased risk of developing cardiomyopathy, conduction abnormalities and sudden death among children with MC. Hence, a careful preoperative cardiovascular assessment with attentive intra-operative monitoring which may include invasive and non-invasive techniques as well as post-operative intensive care are strongly advocated especially in those with cardiac abnormality or pathology.

Despite extensive research, there is no definite curative therapy for MC. These patients only depend on various respiratory chain cofactors supplements (such as co-enzymes Q and various vitamins) for its symptomatic attenuation.

To compound things further, this group of children is also prone to develop malignant hyperthermia (MH) in response to drugs that commonly used in anaesthesia which include succinylcholine and volatile agents.[17,18] As such, special precautions need to be addressed as early as possible particularly in the presence of positive family history of peri-operative sudden death, unplanned intensive care unit admission or unexplained febrile episodes. The institutional protocol of MH must be strictly adhered to, should any of these children present with suspicious evidence which is suggestive of MH.

OTHERS

There are numerous other important anaesthetic implications for syndromic children, such as:

1. Unusual surgical positioning with possibility of musculoskeletal, eye or other soft tissue injury
2. Massive blood loss especially in craniofacial corrective surgeries
3. High risk of gastro-oesophageal reflux
4. Generally malnourished children with greater risk of infection and poor wound healing
5. Challenging post-operative pain management.

In view of these outstanding issues, the collaborative team involved in the peri-operative management should be highly specialized and vigilant of all possible complications of these groups of children.

CONCLUSION

Peri-operative management of syndromic patients constantly challenges the knowledge, skills, and ingenuity of the anaesthesiologist. It is impossible to discuss in depth all the potential problems, but the take-home message for successful anaesthetic management of these patient are careful evaluation of the patient, identify and anticipate the myriad of potential problems as well as thorough understand of the surgical procedure involved. This sub-specialized field would require constant discussion and on-going training among the members of the collaborative team.

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Peripartum Cardiomyopathy

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INTRODUCTION

Heart disease is the second commonest cause of maternal death in UK. Based on data from Confidential Enquiries into Maternal Death (renamed Confidential Enquiries into Maternal and Child Health in 2000), heart disease accounted for 35 deaths in 1997-1999,[1] increasing to 44 in 2000-2002.[2] By combining 3 consecutive triennial reports, it was found that death from cardiomyopathy had tripled from 9 (1982-1993) to 27 (1994-2002).

In the United States, cardiomyopathy in pregnancy and the postpartum period, although rare, accounts for a rising proportion of reported pregnancy-related deaths. During 1979–1984, 3.0% of reported pregnancy-related deaths were caused by cardiomyopathy; this percentage increased to 7.7% in 1991–1997.[3] Cardiomyopathy is one of the few causes of pregnancy-related death that has risen since 1979, 70% of which were due to peripartum cardiomyopathy (PPCM).

PATHOPHYSIOLOGY

Cardiomyopathy is a disease of the heart muscle, a condition in which a ventricle has become enlarged (dilated cardiomyopathy), thickened (hypertrophic cardiomyopathy) and/or stiffened. As a result, the heart's ability to pump is reduced and clinical features of heart failure ensue. Peripartum cardiomyopathy, first described by Demakis in 1991,[4,5] is a poorly characterized, rare form of disorder with peripartum occurrence of left ventricular dysfunction and symptoms of heart failure. Many of the clinical characteristics of PPCM are similar to those of idiopathic dilated cardiomyopathy. However, these two conditions differ in their clinical course and prognosis.

INCIDENCE

The incidence of PPCM is reported to range from 1 in 1300 to 1 in 15,000 live births in the United States,[3] but may be as high as 1:400 in Haiti.[6] The etiology, prevalence, and case-fatality rate for PPCM are poorly understood. Risk factors for PPCM reported in the literature include African descent, advanced maternal age, high parity, twin and higher-order gestation, obesity, gestational hypertension and long-term tocolysis.

ETIOLOGY

The exact etiology of PPCM is unknown, but histological evidence suggests that viral, autoimmune, and idiopathic myocarditis may be responsible.[7] The following are some postulated etiologies for PPCM.

Infectious

Postulate for the infectious cause arises because there is evidence of myocarditis in some patients – one study found the prevalence of myocarditis to be 62% based on histologic findings of endomyocardial biopsy.[8] It is thought that pregnancy causes a decrease in immune response allowing unchecked viral replication, while selenium deficiency may increase cardiac susceptibility for viral infection.

Immunologic

Peripartum cardiomyopathy may be an autoimmune process in which there is abnormal immunologic response to pregnancy. The presence of stress-activated pro-inflammatory cytokines (tumour necrosis factor, interleukin-1) may lend credence to this etiology.[9]

Nutritional

There is an increased incidence of PPCM in malnourished women. It may also be associated with high salt intake, and low selenium levels.

Drug-Induced

There is an association of PPCM with prolonged terbutaline therapy, but it is unclear whether this agent induces cardiomyopathy or simply unmasks subclinical heart disease.

Familial

There have been few reports of familial PPCM, which suggests that it is a form of familial dilated cardiomyopathy unmasked during pregnancy.[10]

DIAGNOSIS

Diagnosis is essentially by exclusion. The diagnostic criteria (Table I) include classic definitions by Demakis in 1991[4] and well as additional echocardiographic features proposed by National Heart, Blood and Lung Institute (NHBLI) in 2000.[11]

TABLE I : Definition of Peripartum Cardiomyopathy

CLASSIC
• Development of cardiac failure in the last month of pregnancy or within 5 months of delivery
• Absence of both an identifiable cause of cardiac failure
• Absence of recognizable heart disease before the last month of pregnancy
ADDITIONAL
Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria
• Ejection fraction < 45%
• Fractional shortening* < 30%
• End-diastolic dimension > 2.7 cm/m^2 body surface area

* Fractional Shortening = $\frac{\text{LV end-diastolic diameter – LV end-systolic diameter}}{\text{LV end-diastolic diameter}}$

The role of echocardiography is threefold – diagnosis, assessment and prognosis. Besides confirming the presence of left ventricular systolic dysfunction and dilatation, echocardiography is also useful for excluding preexisting cardiac disease or other underlying disorders.

Modified dobutamine stress test is used to quantitate LV contractile reserve. While on treatment, echocardiography is used to assess the degree of cardiac dysfunction and response to treatment.[12]

In terms of prognosis, fractional shortening and LV end-diastolic dimension (LVEDD) at the time of diagnosis are predictive of the degree of recovery of cardiac function.[13] In most patients there is evidence of return to normal heart size and function within 6 months of diagnosis and treatment.

MANAGEMENT

Management approach should be multidisciplinary with a clear management plan. Medical management of heart failure follows standard protocols. The obstetrician monitors the fetus and determines the timing and mode of delivery. The anaesthesiologist is involved with ICU management (if indicated) during the peripartum period, as well as anaesthetic management for labour and delivery.

Medical Management

Early diagnosis and initiation of treatment are essential to optimize pregnancy outcome. The therapeutic goals are preload optimization, afterload reduction and increased contractility. Treatment is mainly supportive and includes the standard treatment for heart failure, such as diuretics, vasodilators, digoxin and angiotensin-converting enzyme (ACE) inhibitors.[7,14,15] Due to the risk of

teratogenecity, ACE inhibitors are contraindicated during pregnancy but are the mainstay of treatment in the postpartum period.

The use of α-adrenergic blockade in PPCM has been advocated, as a combination of an ACE inhibitor (enalapril) and a β-blocker (carvedilol) was shown to result in a significant improvement in outcome.[7] Immunosuppressive therapy may be considered in patients with biopsy-proven myocarditis with failed conventional treatment.[14]

Levosimendan, a calcium sensitizer and an inodilator, has been advocated for short-term support of symptomatic low cardiac output heart failure secondary to systolic dysfunction.[16,17] It enhances cardiac contractility by causing conformational changes in cardiac troponin-C during systole, improving the response of cardiac myofilaments to intracellular calcium. It also reduces cardiac workload by opening adenosine triphosphate-dependent potassium channels for dilation of blood vessels, resulting in peripheral and coronary vasodilation. At therapeutic doses, levosimendan exhibits enhanced myocardial contractility with no increase in oxygen demands, unlike traditional inotropes such as β-agonists or phosphodiesterase inhibitors. Successful use of levosimendan in patients with PPCM has been reported.[17]

Complications of PPCM include thromboembolism, dysrhythmias, and heart failure. Additional thromboembolic risks are associated with prolonged bed rest, advanced maternal age, hypokinetic left ventricle, obesity, and pro-coagulant effect of pregnancy itself. As such, anticoagulation is recommended in patients with severe LV dysfunction (ejection fraction < 35%), in atrial fibrillation, with positive history of systemic or pulmonary embolism, or with evidence of mural thrombus. Heparin (unfractionated or low molecular weight heparin), when used, should be timed according to surgery and anaesthesia. Arrhythmias should be treated aggressively, particularly if they are associated with symptoms.

Obstetric Management

In the parturient whose cardiac status has been stabilized with medical therapy, obstetric management includes elective induction of labour at term and the use of low or outlet forceps to shorten second stage of labour. Caesarean section is reserved for the usual obstetric indications. Many patients actually progress to spontaneous labour before term.

Early delivery, while not required in patients with PPCM, may be indicated if medical treatment is unsuccessful and the patient shows clinical cardiac decompensation. The mode of delivery should be assessed in collaboration with obstetricians, cardiologists, and anaesthesiologists. The cardiovascular benefit from prompt delivery is more important whether the delivery is vaginal or abdominal.

Anaesthetic Management

The anaesthetic management of labour and delivery is challenging for patients with PPCM. Due to rarity of the clinical situation, guidelines for anaesthetic management are not well defined and recommendations are based on case reports rather than prospective trials.

As with other types of cardiac diseases, haemodynamic goals include preservation of myocardial contractility, optimization of preload, reduction of afterload, maintenance of sinus rhythm and avoidance of extremes of blood pressure and heart rate (tachyarrhythmias in particular). In view of limited cardiac reserve, a dramatic fall in systemic vascular resistance should be avoided, as this could be catastrophic. These considerations are applicable for labour analgesia as well as surgical anaesthesia for peripartum procedures. Other than routine intraoperative monitoring in the form of ECG, pulse oximetry, capnography, monitoring of invasive pressures in the form of intra-arterial blood pressure and central venous pressure are often indicated. Pulmonary artery catheterization may be necessary in selected patients with poor cardiac function.

a) Analgesia for Labour

Early administration of labour analgesia is desirable to blunt haemodynamic effects of uterine contractions and associated pain response. Central neuraxial blockade in the form of low dose epidural or combined spinal-epidural (CSE) analgesia has been employed successfully in parturients planned for vaginal delivery. Okutomi[18] described the use of continuous spinal analgesia (CSA), and monitored the parturient's cardiac function by means of transthoracic echocardiography. Minimal haemodynamic changes are observed, due to small amounts of local anaesthetic and neuraxial opioid used to provide labour analgesia. Nonetheless, it is prudent to establish close haemodynamic monitoring, including the use of invasive pressures. Vasoactive agents (e.g. nitrates, nitroprusside, dobutamine, dopamine) may be required, and measures for early intervention should be instituted if any haemodynamic derangements occur.

b) Anaesthesia for Caesarean Delivery

Anaesthetic techniques for caesarean delivery, from various case reports in the literature, range from the use of continuous spinal anaesthesia, epidural anaesthesia, low dose sequential combined spinal-epidural anaesthesia and opioid-based general anaesthesia. The choice of anaesthetic technique is influenced by the parturient's haemodynamic and respiratory status, as well as the urgency of surgery.

General anaesthesia is often indicated in the severely ill parturient with tachypnoea, orthopnoea and poor cardiac status. It is also utilised in cases of fetal distress in which urgent delivery of the fetus is warranted. It should be remembered that the anaesthetist's primary responsibility is to the parturient and there should not be undue haste to deliver the fetus if maternal safety is compromised. An opioid-based general anaesthesia in the form of modified rapid sequence induction technique with cricoid pressure and endotracheal intubation is employed. The neonatologist should be present to resuscitate the baby at delivery. Various general anaesthetic agents have been described in the literature. McCarroll[19] used target-controlled infusion of propofol and remifentanil together with rocuromium. Kaufman[20] used sufentanil 50 µg, thiopentone 100 mg, lignocaine 100 mg with suxamethonium; while Pryn[21] used etomidate 20 mg, fentanyl 500 µg with suxamethonium.

Regional anaesthesia may result in catastrophic fall in systemic vascular resistance in parturients with limited cardiac reserve. However, reduction in afterload may improve cardiac function whilst reducing myocardial work as long as the rapid onset of sensory and sympathetic block with associated hypotension can be prevented. As such, the use of single-shot spinal is often not advisable. Techniques of central neuraxial blockade described include epidural,[22] low dose sequential CSE,[23,24] and continuous spinal anaesthesia.[25] It is safer to administer low incremental doses rather than single-shot bolus. However, Pirlet[24] reported a reduction in blood pressure to 65/35 mmHg even with a small intrathecal dose of hyperbaric bupivacaine 5 mg.

PRACTICAL ISSUES

Caesarean delivery should preferably be a planned procedure during office hours to ensure availability of staff and optimal performance. Within the anaesthetic department, there should ideally be a joint management between consultant cardiac and obstetric anaesthetists, as the former can lend expertise with invasive lines, haemodynamic monitoring (including use of transoesophageal echocardiography), and cardiac intervention. In terms of location, it would be logistically simpler for the Caesarean delivery to be conducted in the general operating theatre rather than the obstetric OT, with the advantages of adequate equipment, personnel, and geographical proximity to ICU for ease of transfer.

PROGNOSIS

About half the patients of PPCM recover without complications. Some survivors may not recover

completely and may require mechanical assist device and heart transplantation. Failure of the heart to return to its normal size within 6 months is a poor prognostic indicator.[27] Demakis[5] reported a mortality rate of 14% in patients whose heart size returned to normal compared to 85% in patients who maintained cardiomegaly beyond 6 months.

Mortality of PPCM ranges between 6-56%.[3,26] Earlier figures (> 50% mortality) were based on small number of patients and pre-dated current heart failure therapy. Felker et al[8] reported a low incidence of death (7%) or need for transplantation (7%) in their series. Most deaths occur within 3 months postpartum and are caused by heart failure, arrhythmias, and thromboembolic events.

FUTURE PREGNANCY

The risk of recurrence with subsequent pregnancy is related to the total functional recovery of cardiac function, and future pregnancy is not recommended in women with persistent ventricular dysfunction. In a case series from Haiti, Fett[28] reported that half of the women with subsequent pregnancy after PPCM experienced worsening heart failure and long-term systolic dysfunction, while the other half experienced no deterioration and regained normal left ventricular systolic function. Interestingly, Connelly[29] reported a case of successful pregnancy and delivery in a patient with PPCM who conceived only 3 months after a vaginal delivery complicated by PPCM. It should be remembered that, even with normalization of left ventricular function, the risk of recurrence exists as multiparity in itself is a risk factor associated with PPCM.

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Total Intravenous Anaesthesia And Neurosurgery

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INTRODUCTION

The use of intravenous anaesthetic drug as the sole agent for maintenance of anaesthesia has evolved in the last decade to become a popular alternative to inhalational anaesthesia. This is due to improved understanding of the pharmacokinetics, pharmacodynamics and drug interactions which take place during continuous infusion of IV anaesthetics. In addition, the availability of new computer-assisted infusion pumps that allow precise delivery of anaesthetic and narcotic drugs using integrated pharmacokinetic datasets to control anaesthetic depth can ensure quick awakening even after long hours of anaesthesia. Hence, with these new developments and with the favourable cerebral pharmacodynamic properties of propofol, great interest has been shown in the use of total intravenous anaesthesia (TIVA) for neurosurgery. The purpose of this review is to highlight what some of the studies have shown regarding the use of TIVA in neurosurgery.

IDEAL PROPERTIES OF ANAESTHETIC AGENTS FOR NEUROSURGERY

Anaesthetic drugs used in neurosurgery ideally have the following properties:

- Able to decrease cerebral blood flow
- Able to decrease cerebral metabolic requirement for oxygen ($CMRO_2$)
- Have cerebral vasoconstrictor effects
- Able to decrease intracranial pressure (ICP)
- Preserve cerebral auto-regulation during anaesthesia
- Have anti-epileptic properties
- Should not interfere with evoked potential monitoring used intra-operatively
- Have neuroprotective properties in the presence of brain ischaemia
- Allows rapid and accurate changes in depth of anaesthesia
- Provide stable haemodynamics during induction and maintenance even with lengthy surgery
- Rapid reversal of anaesthesia and return to consciousness

To date, there is no anaesthetic agent that is ideal for neurosurgery. Making a choice based on the available evidence is difficult, as the data from in-vivo studies, in-vitro studies, animal studies and non-blinded trials have various levels of clinical evidence. Some of these findings may not even be applicable in clinical situations. Important considerations in administering anaesthesia for neurosurgery must include the impact of the anaesthetic on cerebral haemodynamics, generating a relaxed brain, enabling haemodynamic stability and quick recovery so that the patient can be assessed immediately postoperatively. Of practical importance is the ease of administering the anaesthetic, cost of drugs and equipment used and safety issues.

CEREBRAL HAEMODYNAMICS OF INTRAVENOUS ANAESTHETICS

It is generally accepted that N_2O is a cerebral vasodilator and can increase cerebral blood flow (CBF) when administered with volatile anaesthetics. This vasodilation can result in an increase in ICP and hence thus worsen cerebral ischaemia.[1-3] All volatile agents are cerebral vasodilators and can increase ICP particularly in the context of decreased cerebral compliance.[4-6] This increase in ICP is significant even when the minimum alveolar concentration (MAC) is as low as 0.5 for isoflurane, sevoflurane and desflurane.[7] However, volatile agents can suppress cerebral metabolic rate (CMR) and produce burst suppression of the EEG in a dose related fashion.

Many studies have demonstrated the beneficial neuron-protective properties of isoflurane in the presence of cerebral ischaemia.[8]

Commonly used intravenous hypnotic agents, with the exception of ketamine, decrease CMR and CBF substantially. In appropriate doses, barbiturates, propofol and etomidate produce burst suppression of the EEG.[9] In addition, not only is the CBF, CBV (cerebral blood volume) and ICP decreased with IV anaesthetics, but auto-regulation and vessel reactivity to CO_2 remains intact.[10] From as early as 1988, studies have indicated that the use of propofol infusion as maintenance anaesthesia was associated with a significant reduction in intracranial pressure while maintaining normal cerebral perfusion pressure.[11] Madson et al[12] studied patients undergoing craniotomy with propofol anaesthesia (12mg/kg/hr) and mechanically hyperventilated to maintain $PaCO_2$ at 33 mmHg. Mean CBF was reduced to 32ml/100g/min (normal value: 40 ml/100g/min) and mean CMR was reduced to 1.4ml/100g/min (normal: 4ml/100g/min).

In addition, propofol has shown to be an efficacious neuroprotective agent in numerous in vivo and in vitro models of cerebral ischemia. These neuroprotective effects of propofol are believed to be due to its ability to attenuate glutamate-mediated excitotoxic mechanisms by either decreasing the N-methyl D-aspartate (NMDA) receptor activation, reducing glutamate release, or recovering the function of transporters responsible for glutamate uptake into neuronal and glial cells.[13]

Patients with severe head injury, cerebral haemorrhage or space occupying lesions may present with very high ICP. The ability of the brain to accommodate further increases in CBV may be exhausted and even slight increases in intracranial volume can result in dramatic increases in ICP and thus poor outcome. Hence, the choice of anesthetic agents must be considered carefully.

EVOKED POTENTIAL MONITORING AND BRAIN RELAXATION WITH IV ANAESTHETICS

All volatile agents attenuate somatosensory evoked potentials (SSEP) in a dose related manner.[14] SSEP amplitude is attenuated at 1.0 MAC and can even be abolished at higher concentrations. Simultaneously, a dose dependent increase in the latency period is also observed. The newer volatile agents sevoflurane and desflurane appear to depress the amplitude of the SSEP to a lesser extent and their use may permit the delivery of a higher concentration (1 – 1.5 MAC) without interfering with neurosurgical procedures requiring SSEP monitoring.[15] Auditory evoked potentials are relatively robust and unaffected by anaesthetic agents but even their waveforms will be affected at volatile anesthetic concentrations that exceed 1.5 MAC. Intravenous agents, on the other hand, have a modest impact on SSEP.[16]

Motor evoked potential (MEP) monitoring is a technique that is being increasingly employed during spine surgery that entails a significant risk of injury to the motor tracts. Transcranial electrical stimulation applied to the scalp is used to depolarize cortical pyramidal tracts and to evoke a motor response in the upper and lower extremities. MEP is also sensitive to anesthetic agents. Volatile agents (in concentrations as low as 0.2-0.3 MAC), barbiturates, propofol and midazolam all significantly suppress MEP.[17, 18]

Given that all anaesthetic agents suppress MEP, the choice of anaesthetic agents for the maintenance of anaesthesia becomes an important consideration. Currently, the combination of propofol and narcotic infusion (without use of muscle relaxants for those requiring MEP) seems the best choice of maintenance anaesthesia for most cases. In addition, the variability in the amplitude of the evoked potential is reduced by this technique in comparison to a N_2O -volatile agent-narcotic technique.[19]

Brain relaxation is important in optimizing surgical conditions for the operating neurosurgeon. In a randomized prospective study[20] of patients subjected to craniotomy for intra-cranial brain tumours, ICP and cerebral swelling at the opening of the dura have been shown to be lower, and mean arterial blood pressure and cerebral perfusion pressure to be higher in patients receiving propofol anaesthesia compared to patients receiving either isoflurane or sevoflurane. When a "tight brain" is encountered peri-operatively and measures to relax the brain fail, it has been suggested that N_2O and volatile agents be withdrawn and replaced with a propofol infusion.[21]

RECOVERY ASPECTS OF TIVA

Studies have shown inconsistent results in the recovery aspects of TIVA when compared to conventional inhalational anaesthesia in neurosurgery. A study by Magni G et al[22] showed no difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanil in patients undergoing craniotomy for supratentorial intracranial surgery. Another study[23] involving neurosurgical procedures lasting more than three hours showed little difference in terms of haemodynamic stability and time to recovery of consciousness when propofol anaesthesia was compared to inhalational anaesthesia. However, Castagnini HE et al[24] showed that sevoflurane was associated with more rapid early recovery compared with propofol when used for interventional neuroradiology procedures.

A prospective study comparing TIVA and inhalational anaesthesia[25] on the incidence of post-operative complications such as shivering, pain, PONV, respiratory problems and neurological problems found that while early postoperative complications were common, it did not show any difference between the two anaesthetic techniques.

PROBLEMS OF TIVA

Even with the advanced technology and increase in knowledge of TIVA, the anaesthetist is still faced with problems when using TIVA. Amongst other things, the need to set up the propofol syringes, programming the perfusor pump and reloading of syringes is cumbersome. Drugs and delivery systems are costly. In a study comparing propofol maintenance and isoflurane for patients undergoing similar supratentorial intracranial surgery,[26] the cost for the propofol group was 6.8 times higher than the isoflurane group.

OUTCOME STUDIES OF TIVA IN NEUROSURGERY

There are few clinical studies to show the impact of anaesthesia on long term outcome and patient mortality following neurosurgical procedures. Despite the theoretical advantages of TIVA, there are few comparison studies that show better long term outcomes for TIVA as compared to inhalational techniques for neurosurgery. In one comparative study,[27] patients with supratentorial intracranial tumors were anaesthetized with propofol-fentanyl, isoflurane-nitrous oxide or fentanyl-nitrous oxide anaesthesia. There was no difference in long term outcome. Consequently, until there are more controlled studies looking at surgical outcome and long term morbidities, it is difficult to make definitive statements on the advantages of TIVA over conventional anaesthesia for neurosurgery.

The author believes that for the majority of patients, it is unlikely that the choice of anaesthetic technique will be substantial enough to influence the outcome of the surgery.

CONCLUSIONS

In reality, all modern anaesthetics are effective and have good safety and tolerability profiles for use in anaesthesia for neurosurgery. Despite the experimental results and the positive effects on cerebral physiology of propofol, no clinical study has yet indicated that TIVA is superior to other anaesthetics in improving the neurological outcome following acute cerebral injury.

Hence it is probably true that in the vast majority of neurosurgical patients, the choice of anaesthetic agent is not relevant as it is unlikely to affect either the surgical field or the patient outcome. The best results are obtained by the use of a technique with which the anaesthetist is familiar with and in the presence of an experienced and skillful surgeon.

In certain situations, however, the choice of the anaesthetic agent may directly impact the surgical field and have an impact on patient outcome. It is during these situations that a strong command of physiology and pathophysiology of the central nervous system and the choice of anaesthetic agent may influence patient outcome.

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Current Views And Uses Of COX-2 inhibitors

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INTRODUCTION

Pain is still at the present time one of the most amazing mysteries which the whole humanity faces. Extracts from the willow tree *Salix alba* have been used since ancient times to relieve pain and inflammation. In 1897 the active compound in these willow herbal remedies was isolated, and Bayer began marketing it as aspirin in 1899.[1,2] Not until the 1960's were other synthetic nonsteroidal anti-inflammatory drugs (NSAIDs) produced. Anti-inflammatory medicines have been available for many years and are important in the treatment of arthritis and other painful conditions. Unfortunately, the use of these drugs is associated with a significant risk of gastrointestinal (GI) complications, including dyspepsia, ulcers, and bleeding. In addition, they can cause generalized bleeding, liver and kidney dysfunction and organ failure, and skin reactions.

All NSAIDs developed before 1990 exert their anti-inflammatory and analgesic (pain-relieving) activity by inhibiting an enzyme, cyclooxygenase (COX). Cyclooxygenase is an enzyme that is responsible for formation of important biological mediators called prostanoids including prostaglandins, prostacyclin and thromboxane. Prostaglandins are potent molecules that help regulate processes in the GI tract, the platelets, and the kidneys. Prostaglandins also promote inflammation and pain in certain diseases and after injury.

CYCLOOXYGENASE 2

In 1991 it was discovered that at least 2 distinct forms ("isoforms") of the COX enzyme exist. There is a constitutive isoform, COX-1, and an inducible COX-2 which is produced after a stimulus.[1,2] COX-1 is expressed in most tissues, regulates physiologic processes such as gastric cytoprotection, kidney function, and platelet aggregation, and is stimulated by growth factors and hormones.[3,4] It is constitutively expressed as a 'housekeeping' enzyme in nearly all tissues, and mediates physiological responses.[3,5] On the other hand, COX-2, expressed by cells involved in inflammation (e.g. macrophages, monocytes, synoviocytes), has emerged as the isoform that is primarily responsible for the synthesis of prostanoids involved in acute and chronic inflammatory states (Figure 1). Among the sites where COX-2 is produced are:

1. In the brain, specifically in the cortex, hippocampus and amygdale;
2. In the female reproductive system where it is associated with ovulation and implantation;
3. In bones where it is associated with osteoblast activity;
4. In the kidney; macula densa, podocytes, and the thick ascending limb, facilitating the regulation of water and electrolyte balance[6-11]

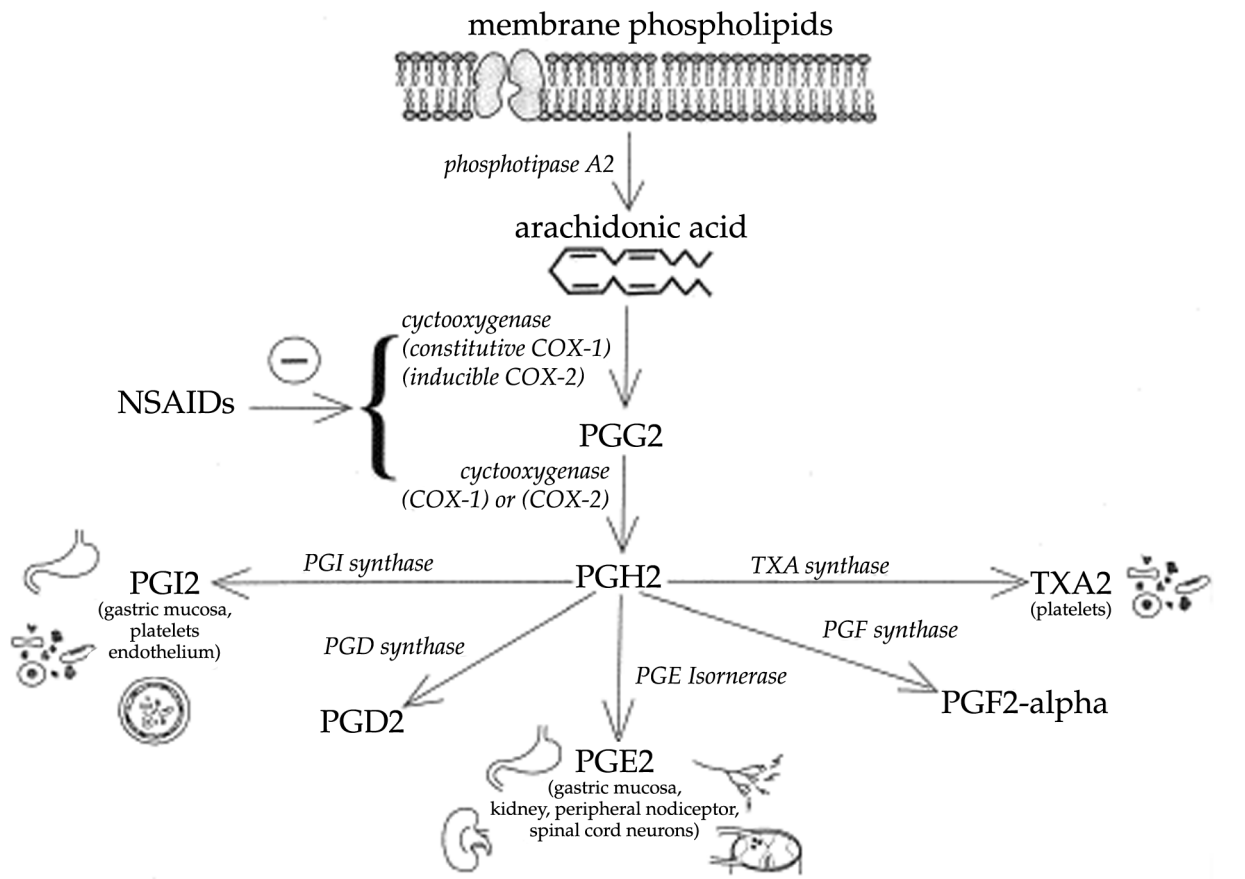

FIGURE 1 : The role of cyclooxygenase in prostaglandin synthesis. Prostaglandins (PGD2, PGE2, PGF2, and PGI2) and thromboxanes (TXA2), which are important in inflammation and homeostasis, are products of a biochemical cascade by which membrane phospholipids are converted to arachidonic acid, then to intermediate prostaglandins (PGG2 and PGH2) by cyclooxygenase, and to their final products by a series of synthases. NSAID : *Nonsteroidal antiinflammatory drug*. Adapted from Myoshi.[15]

COX-2 INHIBITOR DRUGS

Conventional NSAIDs nonselectively inhibit both COX-1 and COX-2. COX-2 inhibitor drugs which were introduced in 1998, had a selective action that provides the benefits of reducing inflammation without the increased risk of stomach irritation, ulceration and bleeding. Another particular advantage of COX-2 inhibitors is that they do not impair the normal function of platelets (Figure 2).

Celecoxib (Celebrex™) and Rofecoxib (Vioxx™) were introduced in 1999 and rapidly became the most frequently prescribed new drugs in the pain treatment replacing the conventional NSAIDs. Findings from study by Sinatra et al[12] on usage of COX-2 inhibitor rofecoxib on patient recovering from midline laparotomy have shown that COX-2 inhibitor drugs:

1. Decrease post operative pain (even in patients using patient-controlled analgesia)
2. Decrease opioid requirement by 20% – 50% and
3. Reduced effect on platelet function and bleeding hence giving advantage for pre- and peri-operative administration

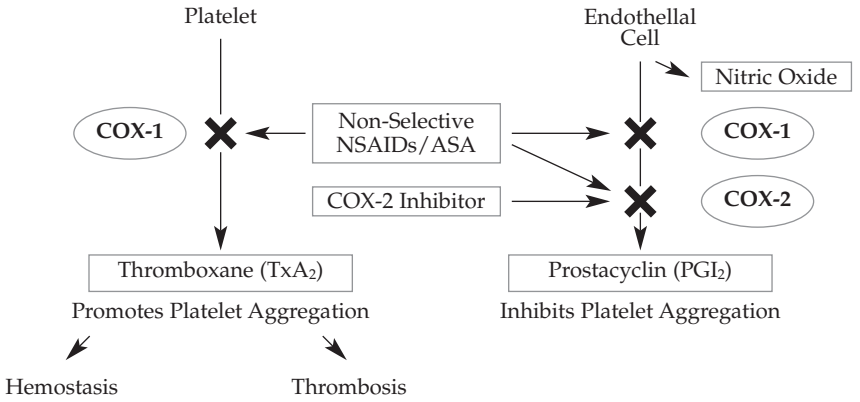

FIGURE 2 : Effect of non-selective nonsteroidal anti-inflammatory drugs, cox-2 inhibitors and aspirin on thromboxane and prostacyclin synthesis.[13]

However, Merck withdrew the blockbuster rofecoxib from the market. This move was in response to new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial. The trial, which has been stopped, was designed to evaluate the efficacy of rofecoxib in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, beginning after 18 months of treatment in the patients taking rofecoxib compared to those taking placebo.

The second generation of COX-2 inhibitors with higher COX-2 selectivity was developed with the promise of further reduction of NSAID-typical adverse effects. The leading compounds are valdecoxib, parecoxib, etoricoxib and lumaricoxib. At the present time they have proven efficacy for the treatment of pain and inflammation. Parecoxib is water soluble sodium salt of the amide prodrug valdecoxib. Currently it is used as a parenteral, highly selective COX-2 inhibitor which has the potential to become the NSAID of choice for treatment of postoperative pain. Etoricoxib shows only a slightly improved COX-2 selectivity than rofecoxib. Lumiracoxib, the most selective COX-2 inhibitor in vitro, is the only acidic coxib. The hypothesis that this chemical property may lead to an increased and persistent drug accumulation in inflammatory sites and consequently to an improved clinical efficacy, however, remains to be verified.[14]

Three mechanisms in the central nervous system are considered important in explaining how COX-2 exerts analgesic effect, which are neuronal plasticity, central sensitization and COX-2 up-regulation. It has been proposed that COX-2 inhibitor drugs prevent central sensitization, therefore giving their analgesic effect. However there have been lingering questions regarding the adequacy of COX-2 drugs in CNS concentration, kinetics and also the optimal duration of postoperative usage. The pharmacokinetics of 3 COX-2 inhibitor drugs are presented in Table 1.

TABLE 1 : Pharmacokinetics of COX-2 inhibitors

COX-2 DRUGS	CELECOXIB	ROFECOXIB	VALDECOXIB
Bioavailability (F)	22 – 40%	93%	83%
(Vd) L/kg	400	91	86
Metabolism	Oxidation	Reduction	Oxidation
Halflife ($t_{1/2}$)	11 hr	17 hr	8 – 11 hr
Chemistry	Sulfonamide	Sulfone (nonsulphonamide)	Sulfonamide

ACUTE PAIN MANAGEMENT WITH COX-2 SELECTIVE INHIBITOR DRUGS – PREEMPTIVE AND POSTOPERATIVE ANALGESIA

The use of COX-2 inhibitor drugs as part of pain management have been widely accepted in current pain practice and anaesthesia. In the perioperative setting, the COX-2 inhibitor drugs offer advantages over nonselective NSAIDs due to their lack of COX-1 inhibition.

Their properties that do not affect platelet function nor do they increase the risk of bleeding combined with prolong duration of action has initiated research on their use in preemptive analgesia. Preemptive analgesic strategies are designed to control or prevent central sensitization, and the rationale for therapeutic intervention considers:

1. Differentiating between analgesic states that eliminate all physiologic pain and those that eliminate only abnormal hypersensitivity.
2. Specifically targeting the induction or maintenance of central sensitization by particular treatments.
3. Preventing or reducing postoperative pain with strategies designed to inhibit the establishment of central sensitization during surgery.

   The use of long-lasting analgesics before surgery may help to avoid the establishment of a sensitized state and result in diminished postoperative pain.[16]

In a study[17] comparing the preoperative analgesic efficacy between rofecoxib and acetaminophen in ear, nose and throat surgery, it was shown that preoperative rofecoxib was significantly more effective than either placebo or acetaminophen ($P < 0.05$); rofecoxib also decreased the need for rescue opioid (fentanyl). Notably, the addition of acetaminophen to rofecoxib did not significantly improve analgesic efficacy.

COX-2–selective inhibitors also have been shown to be efficacious in the prevention of hyperalgesia when used postoperatively as part of a balanced approach to analgesia. Their tolerability and the non-additive nature of the dose-related adverse effects of opioids make the COX-2–selective inhibitors a particularly useful resource in combination with opioids[18] especially with the availability of parenteral parecoxib that can be given before reversal of anaesthesia. In a study[19] of intramuscularly or intravenously administered NSAID for postoperative dental pain, the experimental parenteral coxib, parecoxib, was compared with the nonselective NSAID ketorolac. Although generally comparable on all experimental measures (time-specific pain intensity, pain relief, time to onset of analgesia, and time to use of rescue medication), parecoxib effected a longer duration of analgesia than did ketorolac ($P < 0.05$).

In acute pain, analgesic relief may be dependent on several factors such as time to onset of analgesia, maximum analgesic effect and duration of analgesic effect. Primary dysmenorrhea is caused by prostaglandin-induced uterine hyperactivity and is usually treated with nonselective NSAIDs. The pain associated with dysmenorrhea is similar to perioperative pain, particularly that of abdominal surgery, and lasts about 72 hours. As it is associated with both acute and recurring pain, dysmenorrhea requires analgesic relief on a cyclical basis. Rofecoxib is indicated for the treatment of dysmenorrhea and, at doses of 25 mg or 50 mg, provided analgesic relief comparable to naproxen (550 mg BID) in 127 women with a history of primary dysmenorrhea.[20] Concerns about GI toxicity from the effects of long term nonselective NSAID use are justified.

During a single-dose assessment period (SDAP), celecoxib 200 mg was compared with the combination of hydrocodone 10 mg and acetaminophen 1000 mg, and placebo over 8 hours. The SDAP study data[21] indicated that more patients in the hydrocodone/ acetaminophen arm required rescue medication than the patients taking celecoxib (20% *v* 12%; $P < 0.05$). Furthermore, compared with the patients taking hydrocodone/acetaminophen, the patient group receiving celecoxib had substantially lower pain intensity scores during the 2-5 day period ($P < 0.001$), and required less medication during the 3-5 day period ($P < 0.013$). The patients in the celecoxib arm also experienced fewer adverse effects compared with those in the hydrocodone / acetaminophen arm (43% *v* 89%; $P < 0$ .001). In summary, patients taking celecoxib to control pain following orthopedic surgery experienced superior analgesia compared with those taking hydrocodone/ acetaminophen.

Another study[22] was designed to determine whether the administration of a preoperative dose of celecoxib or rofecoxib to patients who have undergone spinal stabilization would decrease patient-controlled analgesia (PCA) morphine use and/or enhance analgesia. The study showed that both celecoxib and rofecoxib demonstrate an opioid-sparing effect after spinal fusion surgery. Celecoxib resulted in decreased morphine use for the first 8 h after surgery, whereas rofecoxib demonstrated less morphine use throughout the 24-h study period.

MANAGEMENT OF CHRONIC AND CANCER PAIN WITH COX-2 SELECTIVE INHIBITOR DRUGS

Chronic pain is common in people older than 65 years of age. Most people in this age group suffer degenerative bone disease such as osteoarthritis (OA) and rheumatoid arthritis (RA) involving multiple joints especially the hips and knees. More than 40% of treated patients do not achieve satisfactory relief, therefore chronic pain is a public health problem of major proportions.[23] The largely older patient population subjected to chronic pain is also particularly susceptible to the adverse GI effects attributed to regular NSAID use.[24,25]

Numerous clinical trials have shown comparable efficacy between coxibs and nonselective NSAIDs in treating pain and inflammation associated with OA and RA. Treatment with coxibs has resulted in significantly fewer adverse events compared with traditional NSAIDs. In fact, most of the clinical trials indicate that the incidence of GI complications among patients treated with coxibs was similar to that of placebo-treated patients.[23, 26-28]

These studies indicate that COX-2–selective inhibitors provide a viable option for treatment of chronic pain related to arthritis. Furthermore, randomized controlled studies have proven that coxibs (at least rofecoxib) are efficacious at treating the discomfort associated with chronic low back pain.[29]

The World Health Organization (WHO) has developed a stepwise guide to managing pain of increasing intensity which has served as a validated, world-wide standard for the management of cancer pain.[30]

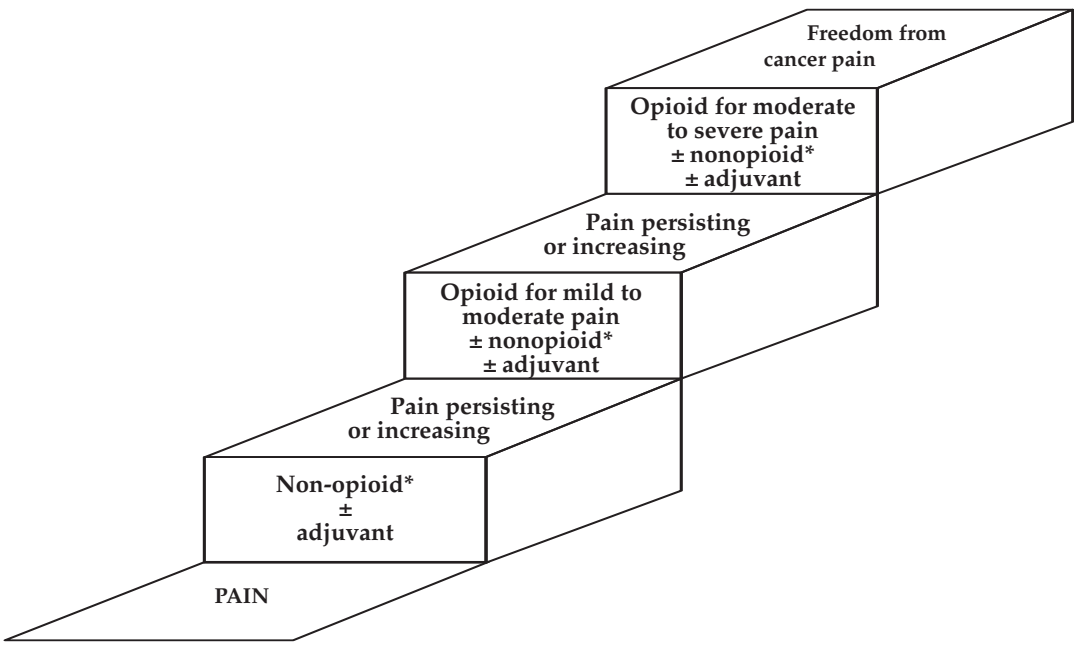

FIGURE 3: World Health Organization "Analgesic Ladder" algorithm for cancer pain management. *NSAIDs/coxibs or acetaminophen. Adapted from: Cancer pain relief and palliative care: Report of a WHO expert committee (Technical Report Series 804). Geneva: World Health Organization; 1990.[30]

The adverse effect of conventional NSAID such as bleeding problems and GI toxicity may make its use unsafe for treatment of certain patients with cancer pain. For example, patients experiencing any bleeding disorder; those who are on anticoagulants such as warfarin, or have hematologic malignancies, or thrombocytopenia after chemotherapy or bone marrow transplant; and those who are being treated concomitantly with chemotherapy or steroids, are all at higher risk of GI ulcers or bleeding complications. Integrating coxibs into the WHO pain-management algorithm for patients with cancer would provide the balanced analgesia endorsed by the WHO algorithm with a lower risk of adverse events.[31]

SAFETY OF COX-2 INHIBITORS

Cardiovascular Event

Cyclooxyenase (COX)-2 selective inhibitors were developed to create a new class of NSAID with properties similar to those of nonselective NSAIDS but without their potential COX-1–mediated gastrointestinal toxicities. Recent evidence also suggests that some doses of the COX-2 selective inhibitors are associated with an increased risk of adverse cardiovascular (CV) events. Reports of a higher incidence of myocardial infarction (MI) among patients with arthritis taking high doses of the COX-2 selective inhibitor rofecoxib compared with those taking the NSAID naproxen[32-34] have had heightened concerns since 2001 regarding selective COX-2 inhibitor safety.

CV event rates among users of NSAIDs, including COX-2 selective inhibitors, have been evaluated in numerous types of studies. The seminal studies that first examined CV events in arthritis populations were the VIoxx Gastrointestinal Outcomes Research (VIGOR)[32] and CeLecoxib Arthritis Safety Study (CLASS) studies.[35-36] CV event rates were higher with rofecoxib 50 mg daily than with naproxen 500 mg twice daily in the VIGOR Trial, whereas they were similar for celecoxib 800 mg daily, ibuprofen 2400 mg daily, and diclofenac 150 mg daily in CLASS. In placebo clinical trials, the Adenomatous Polyp Prevention on Vioxx Trial[37] the APTC (Anti Platelet Trialist Collaboration)[38] event rate was 1.50 events per 100 patient-years for rofecoxib 25 mg daily versus 0.78 events per 100 patient-years for placebo; in the Adenoma Prevention With Celecoxib Trial,[39-40] the combined APTC and heart failure event rate was -0.4 events per 100 patient-years for placebo, 0.86 events per 100 patient-years for celecoxib 400 mg daily, and 1.27 events per 100 patients-years for celecoxib 800 mg daily. Finally, in the Prevention of Colorectal Sporadic Adenomatous Polyps Trial,[41] the estimated rates of adjudicated CV events (MI, stroke, and congestive heart failure) were 0.72 events per 100 patients-ears for placebo and 0.94 events per 100 patient-years for celecoxib 400 mg daily.

The data accumulated thus far suggest that certain COX-2 inhibitors might induce small absolute increases in CV events compared with placebo or non users of the NSAIDs.

Renal Event

NSAID excretion of both parent compounds and their metabolites occurs through renal mechanisms by three kinetic processes: glomerular filtration, tubular reabsorption, and active secretion. Renal events reported with COX-2 include dysuria (celecoxib, valdecoxib, rofecoxib <2%), polyuria (celecoxib, valdecoxib <2%), hematuria (celecoxib, valdecoxib <2%), increased creatinine (celecoxib, valdecoxib <2%), cystitis, azotemia, nocturia, proteinuria, acute renal failure in patients with impaired renal function, renal papillary necrosis, nephrosis, nephrotic syndrome, decreased creatinine clearance, glomerular nephritis, pyuria, oliguria, anuria, urine discoloration, crystalluria, urinary retention, renal stones (celecoxib <2%, valdecoxib <1%), increased CPK and increased BUN (celecoxib, valdecoxib <2%).[42]

As with all NSAIDs, the COX-2 agents valdecoxib, celecoxib, and rofecoxib should be used with caution in such patients, in patients especially with preexisting fluid retention, hypertension, or heart failure.[43-45]

CONCLUSION

COX-2 selective inhibitors are a relatively new class of antiinflammatory agents that have several advantages over traditional NSAIDs for certain populations. COX-2 inhibitors, unlike nonselective NSAIDs, do not impair platelet function or increase bleeding time,[46]

and do not increase blood loss.[47] However its usage is not indicated in the paediatrics age group, pregnant and breast feeding mothers. Nevertheless with the introduction of COX-2 selective inhibitors, the incidence of GIT bleeding or perforation is grossly reduced and its usage as preemptive analgesia have revolutionized the postoperative pain management in patients. Furthermore its properties which do not impair conscious level or respiration can initiate studies in patients with impaired Glasgow Coma Scale and respiratory problems unlike opioids.

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Intubating The Ill Patient

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INTRODUCTION

In contrast to a more conducive environment offered by operating room conditions, securing the airway in a critically ill patient in the intensive care unit or remote locations is a different ballgame altogether. In these emergency conditions, there is lack of time to draft contingency plans if the first plan falls through. Airway assessment is often performed in the most cursory manner. The various airway adjuncts for difficult intubation are often unavailable in these locations. Specialist help is a distance away and life can be lost while waiting for help to arrive. In contrast to elective surgery, the patient cannot be reversed and made to come back another day. Furthermore, whether intubation is successful or unsuccessful, the airway needs to be secured by whatever means in patients who are often at risk for aspiration. All these factors combined require that an anaesthetist remain astute when facing these critical conditions. It is rather surprising therefore, that airway management is not given as much attention in the ICU as compared to the operating theatre environment.

Various articles have been published highlighting various aspects of airway management in intensive care and remote locations. This review attempts to address various issues raised in the literature for the benefit of the anaesthetic medical officer who is managing the difficult airway in this environment. The author would like to further emphasize that some of the views expressed in this review are the personal views of the author.

INCIDENCE OF DIFFICULT AIRWAY AND PREDICTING THE DIFFICULT AIRWAY IN CRITICALLY ILL PATIENTS

The incidence of difficult intubation is reported to be 1 in 2230 in anaesthesia, increasing to 1 in 300 in the obstetric population.[1] Whether or not one finds this a comforting figure, it does not apply to the critically ill population. The incidence of difficult intubation in the intensive care setting was found to be 8% by Schwartz et al,[2] 12% by Jaber et al[3] and more than 20% in a paper by Le Tacon.[4] The differences in incidences reported could be due to dissimilarities in defining the difficult airway and whether the series involved intubation that occurred in the ICU or included those in remote locations. The point to note, however, is the discomforting fact that whichever figure one chooses to accept, all are sharply higher than that quoted even for the obstetric population.

In general, difficult intubation is defined either by the number of attempts required to successfully intubate the patient (usually more than two attempts),[2,3] the duration it takes to perform the intubation or if there was a need for another operator.[3] Needless to say, all these are strongly affected by the level of experience of the operator. Schwartz studied all patients requiring intubation in the ICU and found that more than 25% of these patients underwent more than one attempt before they were successfully intubated.[2]

Is there a reliable way of predicting difficult intubation in the critically ill patient? In most instances, airway assessment is not done and difficult airway is only predicted if there are obvious facial abnormalities or morbid obesity. In complaints related to respiratory events in Denmark,[5] difficult intubation was not anticipated in 10 out of 15 difficult intubations. It may be impractical to properly assess the airway in a collapsed patient. Unfortunately, this habit has somehow been 'extrapolated' to all critically ill patients, even in those who are able to cooperate with airway assessment. Le Tacon[4] in his paper concluded that Mallampati scoring is in fact useful (the only useful factor) in predicting difficult intubation in ICU patients.

Although it is understandable that in these situations one can never reverse patients and bring them back another day, the safest practice is still to attempt to perform the usual assessments such as Mallampati scoring, thyromental distance, mouth opening, assessment of dentition and neck mobility in all ill patients who require emergency intubation. If a difficult airway is predicted, help can be arranged beforehand, back up plans can be put in place and adjuncts such as supraglottic airways, bougies and special laryngoscopes can be obtained. In severe situations where the airway is predicted to be difficult and the patient's condition permits, intubation can be done in the safer and more controlled operation theatre environment. The safety culture so carefully nurtured in an anaesthetist practising in the operation theatre should also be extended to the intensive care environment.

Are critically ill patients difficult to mask ventilate? Evidence is probably unnecessary for one to answer in the affirmative. The patient may be oedematous, the face mask fits poorly and the bag valve mask may not work properly. A recent correspondence to the New England Journal of Medicine in 2007[6] highlighted that various studies had found radiographic evidence that the soft palate and the epiglottis rather than the traditionally blamed tongue was a frequent cause for airway obstruction during bag valve mask ventilation. An oropharyngeal airway may or may not help make things better. A supraglottic device often works better giving a better facial seal and reducing gaseous distention of the stomach.

Is there a way that we can reduce the incidence of difficult intubation? Le Tacon[4] had suggested that the development of airway management protocols in the intensive care may reduce the incidence. Mort[7] went on further to compare two periods, before and after the incorporation of the American Society of Anaesthesiologists (ASA) difficult intubation guidelines in remote locations. If one were to fully follow the recommendations made by the ASA on Management of the Difficult Airway, there must be immediate access to advanced airway devices and endotracheal tube-verifying devices by the bedside at all intubation encounters regardless of the venue and this was in fact implemented by Mort. The paper demonstrated that this step had reduced the incidence of cardiac arrest following intubation by 50%. It also reduced the incidence of regurgitation and aspiration by 55% and 67% respectively.

In the typical Malaysian government hospital setting, intubation in remote locations is usually done by non-specialist members of the team. These doctors who are given the task of intubating patients outside the ICU environment have to manage in awkward situations (examples include fixed height of the bed, poorly positioned head, poorly functioning suction apparatus, absence of stylet, lack of oxygen outlets and absence of airway trained assistant) and have little equipment to prepare in the event that a difficult airway is encountered. This situation can be improved if doctors performing intubations in remote locations carry a case which is equipped with various sizes of endoctracheal tubes, stylets, supraglottic airway devices (e.g. laryngeal mask airway or Proseal™, bougies and laryngoscopes).

Are there concerns about who is performing the intubation and does this affect the incidence of difficult intubation? Jaber et al[3] found there to be no difference in incidence between by anaesthesiologists and nonanaesthesiologists although there may be concerns about extrapolating this to centres other than the one in which the study was conducted.

MORTALITY AND OTHER COMPLICATIONS DURING INTUBATION IN INTENSIVE CARE

Schwartz found that the incidence of mortality during or within 30 minutes after intubation to be about 3%.[2] In more than half of these patients there was preexisting systemic hypotension, whether or not vasoactive support was required. This was the only predictor of death following intubation in this series.

In the paper written by Mort in 2004[7] in which more than 3000 patients were studied, the incidence of cardiac arrest associated with intubation in the ICU population was found to be 2% (1 per 50 cases). The author made a few important points in his conclusion; that this is in contrast to the incidence of cardiac arrest during intubation in anaesthesia which was about 0.02 to 0.05% (about 100 fold less) and that

the most important risk factor associated with this complication was profound hypoxaemia (arterial saturation less than 70%) during the airway procedure. Hypoxaemia occurred in 83% of the arrest cases. He also observed that in sharp contrast, arrests which occur in the OT were usually due to poor ASA physical status (III and IV), the extent of the surgical procedure, extremes of age and emergency surgery. Respiratory-based cardiac arrests occur only at a rate of 1 case per 10,000 anaesthetics in the OT environment.

If the incidence of rapid desaturation could be decreased in the OT through adequate preoxygenation, the situation in critically ill patients is drastically different. In another paper by Mort,[8] 14 out of 60 patients who arrested in the ICU population failed to have pulse oximeter readings increased to greater than 90% despite vigorous attempts and as expected these patients had rapid reductions in pulse oximetry readings during laryngoscopy. A patient who requires intubation in the ICU frequently have poor oxygenation to begin with, and although some attempt should always be made to improve the oxygen reserve in the lungs prior to induction, doctors need to be acutely aware of the limitations of preoxygenation in critically ill patients. In his discussion, Mort indicated that there is little benefit of this manouvre in patients who need intubation for cardiopulmonary causes although it was found to beneficial in patients needing intubation for airway protection. The paper still concluded with the recommendation that preoxygenation be routinely performed for all patients but an effective way of doing this needs to be found.

The risk of oesophageal intubation is also sharply higher in the ICU population. Schwartz et al[2] observed an incidence of 8% in 297 intubations done at their centre. Less than half occurred in patients who met criteria for difficult intubation, meaning that even in apparently straightforward intubations, the tube is often inadvertently placed in the oesophagus. Most of these were recognized through auscultation of breath sounds and gastric distension, but in about 10%, this complication was only recognized when there was a decrease in haemoglobin saturation via pulse oximetry. The attendance of a supervising specialist did not reduce the incidence in this series.

There was also a 4% incidence of aspiration in these patients although cricoid pressure was applied and many were not considered to have full stomach. The author also correctly observed that this manouvre is probably unknown among non-anaesthesiologists and does not seem to affect the incidence of aspiration in the intensive care unit. Mortality in these series was found to be 3%, occurring mostly in patients with associated hypotension (systolic pressure < 60mmHg) or patients who were on vasoactive drugs; despite the fact that there were no sedative or hypnotic agents given for the intubation. The mortality of patients during intubation was found to be increased to 15% versus less than 1% with the presence of hypotension. The authors postulated that the institution of positive pressure ventilation may have further decreased venous return to the heart.

There is a strong relationship between oesophageal intubation and cardiac arrest as more than half (62%) of the patients who arrested in Mort's series were intubated oesophageally.[7] He reported a sharp decline in the number of arrests as well as other respiratory complications such as multiple oesophageal intubations and multiple attempts at intubation when the ASA algorithm for difficult airway management was incorporated in the remote location.

Jaber et al[3] in a French study involving 253 patients found the rate of complications related to endotracheal intubation to be 28%. The list of complications listed were severe hypoxaemia, haemodynamic collapse, cardiac arrest, difficult intubation, arrythmias, oesophageal intubation and aspiration. He found that shock and acute respiratory failure were predictors of these complications. In contrast to what was reported by Schwartz, these investigators found that two operators during intubation were protective against the complications listed above.

In summary, the incidence of complications while intubating the critically ill patient can be as high as 28%. The most common complications were oesophageal intubation with resulting aspiration, cardiac arrest, haemodynamic collapse and arrythmias. Sophisticated techniques of confirming correct ETT placement is generally unavailable in our setting, so vigilance must be increased and this

complication actively excluded even in a patient who was easy to intubate. In all critically ill patients who are intubated, an improvement in the patient's colour and presence of the pulse must be confirmed immediately after intubation. Failure to improve oxygenation or persistence of cyanosis following intubation could indicate incorrect placement of ETT or that cardiac arrest has occurred. Another common cause for failure to improve oxygenation following intubation that has been observed by the author is inadvertent failure to administer oxygen to the patient and a conscious effort must be made to avoid this problem.

CHECKING FOR CORRECT PLACEMENT OF ETT

If oesophageal intubation is so common despite apparently straightforward intubations, what then is the most reliable technique for confirming correct ETT placement in the intensive care setting? Direct visualization of the ETT passing between the vocal cords is said to be the gold standard but is not always possible and the tube can still be dislodged following correct placement. Presence of vapour in the ETT is one of the most unreliable but frequently sought after sign. Its place is not established in the literature and its usage as a confirmatory sign potentially dangerous. In a study conducted in dogs by Kelly et al,[9] vapourisation occurred 100% of the times when the ETT is placed in the trachea but also occurred 83% of the times when the tubes were in the oesophagus. Although this study was not conducted in humans, this supports the suspicion that this technique has no place in high stakes decision such as this.

Knapp et al[10] compared four different methods of verifying tracheal tube placement in intensive care patients. The four methods being compared included capnography, auscultation at the infraclavicular, midaxillary line and the epigastrium, eosophageal balloon dilatation method and transillumination method using the Trachlight™. In this study, a comparison was also made between experienced staff and junior doctors. The findings indicated that the only technique which was correct 100% of the time regardless of the experience of the assessor was the capnograph. Although it may be the next gold standard in excluding placement of the ETT into the oesophagus, there are a few outstanding issues with regards to its routine use. It is not universally available and is unreliable in cardiac arrest and severe hypotension as the detection of carbon dioxide depends on an intact pulmonary circulation. In these situations, a technique which is not dependent on an intact pulmonary circulation such as oesophageal detection method (EDM) is suggested by the authors to be superior. This technique, which also not failsafe, involves connecting a compressed self inflating bulb or alternatively a syringe to the in-situ endotracheal tube. Rapid reinflation (less than 4 seconds) of the bulb indicates tracheal placement while delayed reinflation or no reinflation indicates that the tube is placed oesophageally. Tracheal illumination using the Trachlight™ has a similar degree of maldetection in recognising the tracheal glow, in both experienced and inexperienced doctors, and is probably suitable only to one highly experienced in its use.

In most instances, auscultation of the lungs and the epigastrium is the standard if not the only test done, and this practice is likely to continue for its universal availability. Unfortunately, as supported by the study conducted by Knapp et al,[10] this is also the only technique found to be strongly affected by the level of experience of the observer. In this series, experienced doctors correctly diagnosed ETT placement 100% of the time, while their less experienced counterparts were correct only 68% of the time. The irony lies in the fact that this test is also likely to be the only confirmatory test familiar to the latter.

Birmingham and colleagues in 1986[11] wrote a review on methods of detection of inadvertent oesophageal intubation when the capnograph was not yet routinely available even for anaesthetic use. Even then its potential in this area was well recognized. The following methods were among those identified in this paper as commonly used techniques: cuff palpation, observation of chest movements, reservoir bag compliance and refilling, detection of expiratory tidal volumes by the ventilator and chest radiography. None of these methods were found to reliably exclude oesophageal intubation.

Perhaps two highly confirmative but impractical tests will include visualization via fibreoptic bronchscopy and ultrasonography.[12] These tests are of high value but has low practicality in terms of availability, cost and the need for expert handling and therefore unlikely to be routinely used in the near future, especially in remote locations.

Apart from inadvertent oesophageal placement, the other common form of incorrect placement is endobronchial placement. The tip of the endotracheal tube should be placed at 5 ± 2 cm above the carina.[13] Again auscultation is frequently used as the technique of choice. The main problem with this technique is that the unequal breath sounds and chest rise could occur as a result of lung pathology. As such, a more definitive test is indicated in the intensive care setting. A few suggested techniques include palpation of the cuff in the suprasternal notch, fibreoptic confirmation, radiographic views, tracheal illumination[13] and ultrasound techniques.[12] Each of these tests has their limitations either in terms of sensitivity, cost or practicality.

MANAGING THE PATIENT IN RESPIRATORY DISTRESS WITH KNOWN/ANTICIPATED DIFFICULT INTUBATION AND OTHER ROLES OF SUPRAGLOTTIC AIRWAY DEVICES

What if the patient is known to have difficult intubation e.g. Grade IV on previous intubation but is now in respiratory distress requiring urgent intubation and mechanical ventilation? What options are left and what would be safest technique of intubation for the patient? Cook et al[14] in a case report of two patients described how a Proseal™ laryngeal mask airway was used to ventilate these patients with anticipated difficult airway and subsequent percutaneous tracheostomy performed while ventilation continued with the device. In another report, an unanticipated difficult airway was managed the same way.[15] The potential use of these supraglottic devices in the ICU setting in anticipated or unanticipated difficult airway as a bridge to percutaneous tracheostomy is further supported by many papers reporting elective use of laryngeal mask airways for airway control during the procedure.[16-20]

There have also been case reports of supraglottic airways being used as the definitive airway itself. In these reports, endotracheal intubation was abandoned following failed attempts and ventilation was achieved using the supraglottic devices for the entire duration of the mechanical ventilation.[21,22]

Supraglottic airways are also thought to be better at preoxygenating patients who fail to improve with mask ventilation.[23] There are also multiple reports of laryngeal masks being used to facilitate weaning from mechanical ventilation in patients when the weaning process was complicated.[24-26]

EXTUBATING THE PATIENT WITH DIFFICULT AIRWAY

What is the safest method for extubating the patient who was known to be difficult to intubate? The incidence for reintubation in the intensive care setting is said to range between 5 to 19%,[27] which means that up to one in every five patients extubated will need to be reintubated. In a series of postoperative maxillofacial and neck surgery patients conducted in Turkey, the paediatric airway exchange catheter was routinely left inside the trachea during extubation to facilitate railroading of the ETT for reintubation.[28] In these patients, laryngoscopic intubation is almost always impossible and there is likely to be difficulty in performing fibreoptic intubation or even in using surgical airway as rescue techniques. The other advantage offered is that this device will also permit oxygen insufflation as well as jet ventilation. Despite this, caution must be exercised in assuming that this is a failsafe technique as failure to railroad is not uncommon in which there will be a need to have other back up plans. The authors claimed that this approach had reduced the need to perform elective tracheostomy in these patients, which was previously the usual practice.

Common practices when faced with this issue include delaying extubation of the patient until the risk of the patient requiring reintubation is minimized and performing an elective tracheostomy prior to weaning from mechanical ventilation.

WHAT'S NEW IN AIRWAY MANAGEMENT IN INTENSIVE CARE?

There is no doubt that new techniques, new devices or new uses of old devices will continue to be researched in this area although most of them do not automatically result in a change of practice. Examples of new uses of old devices include the role of ultrasound in airway management. Sustic[12] wrote an interesting review which highlighted the many uses of the ultrasound in this area. Ranging from preintubation assessment to predict difficult intubation, including facilitating the detection of tumours, abscesses or epiglottitis, it can then be used following intubation to verify correct ETT placement and exclude endobronchial and oesophageal placement. In instances where a double lumen tube (DLT) needs to be used, it can be used to gauge the appropriate size of the DLT to use, to confirm correct placement as well as confirming successful one lung ventilation.

For procedures such as percutaneous tracheostomy and cricothyrodotomy, the ultrasound can be used to identify the optimal site for the procedure and identification of vascular structures that may cause complications. It can take the place of bronchoscopy as an aid during the procedure itself and can be used post procedure to confirm correct placement.

Other uses of the ultrasound include confirming correct placement of the LMA where it is important to ensure that the tip is correctly placed in the upper oesophageal sphincter for maximal protection against aspiration and to predict extubation failure by gauging adequacy of diaphragmatic function.

CONCLUSION

Airway related problems in the ICU is as old as the specialty itself and will continue to be a familiar encounter to those who has entered its practice. How much or how little is done to circumvent and prepare for the eventuality varies between different locations and as well as between individuals within the same location. The author would like to reiterate that contrary to popular belief, lack of preparation is not always dictated by urgency or feasibility. The respect given to the airway in the operation theatre should similarly be extended to the intensive care and remote environments when intubating the ill patient.

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Predicting Fluid Responsiveness In The Critically Ill

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INTRODUCTION

Fluid management is an important aspect in the management of the critically ill. Volume expansion is frequently used to improve haemodynamics in these patients. The expected haemodynamic benefit of volume expansion is an increase in left ventricular stroke volume, and hence in cardiac output. However, only 52% of patients with acute circulatory failure respond to volume expansion.[1] Fluid challenge is also potentially risky. Inappropriate fluid loading may cause fluid overload, pulmonary oedema, interstitial fluid sequestration, increased tissue hypoxia and haemodilution. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, the risk of death was increased by 10% for every litre increase in cumulative fluid balance within the first 72 hours of sepsis.[2]

Cardiac preload is commonly affected during acute circulatory failure. The relationship described by Frank and Starling between preload and stroke volume is not linear, but rather is curvilinear. According to the Frank-Starling relationship, an increase in preload will induce a significant increase in stroke volume only if the ventricle operates on the steep portion of the curve (condition of ventricular preload dependence) than if the ventricle operates on the flat portion of the curve (preload independence). *Refer Figure 1*. There is another condition to be fulfilled when administering fluid to improve cardiac preload and ultimately stroke volume. The fluid infused has to reach the heart chambers to significantly increase cardiac preload. In conditions where there is increased venous pooling, increased venous capacitance or capillary leakage, fluid therapy may not improve stroke volume in these conditions.

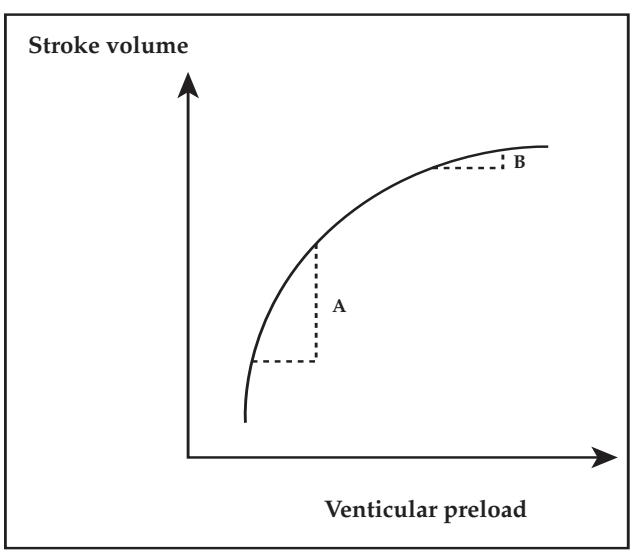

FIGURE 1 : Frank–Starling relationship between ventricular preload and stroke volume.
A : Condition of preload dependence
B : Condition of preload independence

There is a need for reliable predictive indices of fluid responsiveness in order to select patients who could benefit from volume expansion and to avoid ineffective or deleterious fluid therapy in the non-responders. Haemodynamic parameters available as indices of fluid responsiveness can be divided into static and dynamic indices.

STATIC PREDICTIVE INDICES OF FLUID RESPONSIVENESS

Measurements of intra-cardiac pressures or ventricular volumes are known as static indices. These parameters have been used frequently to predict fluid responsiveness.

Intra-Cardiac Pressures e.g. RAP And PAOP

Right atrial pressure (RAP) is assumed to reflect the right ventricular filling pressure. Several studies have shown that there is no difference in mean values of RAP before and after volume expansion in responders and nonresponders.[3-5]

When used correctly, pulmonary artery occlusion pressure (PAOP) can be used to reflect left ventricular (LV) preload. A few studies have showed no relationship between the pre-infusion PAOP and the haemodynamic response to fluid.[3-7] In one study, the pre-infusion PAOP value was lower in responders but the correlation between PAOP and the increase in stroke volume was weak.[8] No cut-off value was found to discriminate responders and non-responders to volume expansion.

RAP and PAOP are not accurate indices of fluid responsiveness. This is because it is the transmural, and not the intra-cavitary pressure that is related to end-diastolic volumes via its ventricular compliance.

Ventricular End-Diastolic Volumes e.g. RVEDVI, LVEDVI, GEDVI

In 4 out of 6 studies, right ventricular end-diastolic volume index (RVEDVI) was not significantly lower in responders than in non-responders before fluid therapy.[3,4,9,10] Two other studies by the same author reported lower values of RVEDVI in responders than in non-responders.[6,11] He suggested that a patient is likely to be fluid responsive when RVEDVI is very low (< 90ml/m^2) and very unlikely to be responsive when RVEDVI is very high (> 138ml/m^2). However, no cut-off value was found to discriminate between responders and non-responders when RVEDVI ranged between 90 and 138ml/m^2.

Left ventricular end-diastolic area (LVEDA) which can be measured by echocardiography is often used as a surrogate of left ventricular end-diastolic volume (LVEDV). In two studies, the LVEDA before volume expansion was significantly lower in responders than in non-responders.[7,8] However, one study[7] demonstrated poor discrimination between responders and non-responders when the data were analysed using the receiver operating characteristic (ROC) curve, while the other study[8] showed marked overlap of baseline individual LVEDA values in responders and non-responders. So a given value of LVEDA could not be used to predict the haemodynamic response to fluid infusion.

Similarly, Michard[12] showed that there was marked overlap of baseline values between responders and non-responders when global end-diastolic volume index (GEDVI) was used to predict fluid responsiveness. GEDVI was useful for predicting fluid responsiveness only when the values were very low (< 680ml/m^2) or very high (> 800 ml/m^2) where the percentage of responders to volume loading was 77% and 23% respectively.

Static indices of preload such as intracardiac filling pressures and ventricular volumes have been found to be useful to confirm that the fluid infused has reached the cardiac chambers. Because the preload-induced changes in stroke volume also depend on cardiac contractility and afterload, these static indices do not reliably predict fluid responsiveness as a given value may be associated with preload dependence in normal hearts or with preload independence in failing hearts.

DYNAMIC PREDICTIVE INDICES OF FLUID RESPONSIVENESS

Dynamic parameters of preload involve heart-lung interaction. In deeply sedated patients who are mechanically ventilated, positive pressure ventilation cyclically increases intrathoracic pressure and lung volume. The cyclic changes in LV stroke volume are

mainly related to the inspiratory decrease in RV filling and output causing expiratory decrease in LV preload. Therefore, the LV stroke volume is maximum at the end of the inspiration and minimum two to three heart beats later due to blood pulmonary transit time (i.e. during expiration). The positive intrapleural pressure may also induce squeezing of blood out of alveolar vessels, and thus transiently increase LV preload. The inspiratory increase in pleural pressure may also decrease LV afterload and thus facilitate LV ejection.

The presence of these cyclic variations indicates that any variation in preload would induce a variation in stroke volume and that volume expansion would increase stroke volume and cardiac preload in preload-dependence situation. This dynamic parameter of respiratory variation is known as stroke volume variation (SVV). Stroke volume variation is the ratio of the difference between the maximum and minimum SV and the mean SV.

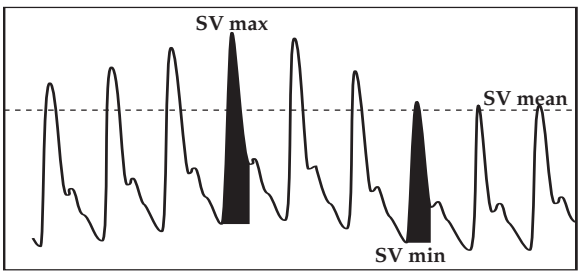

FIGURE 2 : $SVV = \frac{SV\ max - SV\ min}{SV\ mean}$

SVV can be measured directly using transoesophageal echocardiography. Other techniques of measuring SVV include oesophageal pulsed Doppler or by the arterial pulsed contour technique. Berkenstadt[13] studied the accuracy of SVV as a predictor of fluid responsiveness in patients undergoing brain surgery. The sensitivity and specificity were 79% and 93% respectively when SVV of 9.5% was taken as the cut-off value. Different techniques of measurement have shown conflicting results.[14, 15]

The surrogates of SVV include systolic pressure variation (SPV), pulse pressure variation (PPV) measured using an arterial catheter or descending aortic blood flow variation e.g. descending aortic blood velocity, diameter of descending aorta which can be measured by echocardiography.

Pulse pressure depends on stroke volume and arterial compliance. The reliability of PPV as a surrogate for SVV was studied by many authors.[16-19] Reuter[17] found that effects of volume resuscitation on cardiac output can be monitored by parallel changes in SVV and PPV in mechanically ventilated patients after cardiac surgery. Similarly, Hofer[19] found no significant difference between PPV and SVV in prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting.

Respiratory variation of dynamic parameters has been demonstrated to be reliable markers of fluid responsiveness in mechanically ventilated patients. However, in the presence of spontaneous breathing, the indices of fluid responsiveness that use heart-lung interactions such as PPV and SVV are no longer reliable. In patients who are ventilated with low tidal volumes (less than 8ml/kg), the small pleural pressure change will not induce a significant change in LV stroke volume and therefore limits the use of the respiratory variation of dynamic indices in most patients in the intensive care units who are now ventilated with low tidal volumes. In the presence of cardiac arrhythmias, the beat-to-beat variation in stroke volume and blood pressure also no longer reflect the effects of mechanical ventilation on these dynamic indices.

PASSIVE LEG RAISING AND DYNAMIC PREDICTIVE INDICES OF FLUID RESPONSIVENESS

Fluid challenge is associated with certain risks particularly pulmonary oedema. Passive leg raising test which involves the elevation of both the lower limbs from the horizontal plane to an angle of 45° in relation to the bed has been proposed as an alternative to fluid challenge. It is a simple bedside test used to cause a transient increase in cardiac preload by shifting about 300 ml of blood from the lower limbs to the intrathoracic compartment. In a study by Boulain,[20] passive leg raising induced a significant increase in PPV, PAOP and stroke volume. This has

been demonstrated to be a possible valuable tool for predicting fluid responsiveness in some studies. However, in severe hypovolemia, blood volume mobilised is small and does not change SV even in responders. Due to the short-term effects of passive leg raising, the method of measurement need to be automatic to be able to capture beat-to-beat stroke volume or cardiac output.

Monnet et al[21] showed that when passive leg raising induced an increase in aortic flow measured using oesophageal Doppler of more than 10%, it was predictive of an increase in aortic blood flow of more than 15% in response to volume expansion with sensitivity of 97% and specificity of 94 %. Twenty two of the 71 responders were on spontaneous breathing mode on ventilators. They also showed that PPV of ≥ 12% in response to passive leg raising test was predictive of an increase in aortic blood flow by more than 15% in response to volume expansion.

Passive leg raising which is a simple bedside manoeuvre used to increase cardiac preload has been demonstrated to be a valuable tool for predicting fluid responsiveness. This dynamic method remains reliable in patients with mechanical ventilation regardless of their cardiac rhythm and their own breathing activity.

SUMMARY

Static indices of cardiac preload regardless of their methods of measurement are poor indicators of preload dependency and thus are poor predictors of fluid responsiveness.

Respiratory variation of dynamic parameters are reliable predictors of fluid responsiveness in mechanically ventilated patients who do not have spontaneous breathing efforts or cardiac arrhythmias.

Combining the information provided by the static indices of cardiac preload and the dynamic indices of the slope of the Frank-Starling curve is probably the best option in the decision making process concerning volume expansion.

Passive leg raising can be considered to be a valuable tool for predicting fluid responsiveness. This dynamic method remains reliable in patients on mechanical ventilation regardless of their cardiac rhythm and their own breathing activity.

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Septic Shock: A Heart Breaking Story

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"The heart has reasons that reason does not understand."

Jacques Benigne Bossuet

INTRODUCTION

The relationship between septic shock and the heart had been observed way before the American College of Chest Physicians and Society of Critical Care Medicine introduced their definitions for sepsis and organ failure in 1992.[1] Waisbren in 1951 described a group of patients who were profoundly hypotensive with low volume pulses, following Gram-negative bacteremia.[2] They were different and were much more ill than the larger group of patients who presented with the typical hyperdynamic state of full bounding pulses.

Subsequent similar observations and related works in the subject of septic shock further advanced the understanding of its cardiovascular manifestations. It was recognised that the heart, in the presence of adequate circulating volume, did not necessarily increase its performance to compensate for the dilated peripheral circulation in sepsis. Today, the phenomenon of myocardial depression in septic shock is central to numerous intensive care studies.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Despite optimization of blood pressure and preload, Parillo and coworkers[3] demonstrated that 10 to 15 % of septic shock patients had myocardial depression that necessitated inotropic support. Similar incidence was also repeated in a number of other studies, including the early goal directed therapy (EGDT) study by Rivers and colleagues.[4-6] Studies looking at ventricular dimensions, via ventriculograms or echocardiogram, revealed interesting yet conflicting manifestations of this myocardial depression. Parker and coworkers[7] found that survivors of septic shock had a decreased left ventricular ejection fraction (LVEF) and an increased left ventricular end diastolic volume index (LVEDVI), the latter indicating dilated left ventricle. These changes returned to normal after 7 to 10 days. Nonsurvivors, on the other hand, interestingly maintained normal LVEF and LVEDVI until death. The authors postulated that the low systemic vascular resistance index (SVRI), a presentation not seen in the survivors group, contributed to their normal LVEF despite a reduced myocardial contractility. The trends observed in this study were however contradicted by results of another comprehensive study[8] employing both transoesophageal echocardiography and invasive monitoring to evaluate myocardial performance in septic shock. The results revealed that patients with lower left ventricular fractional area contraction (LVFAC) had worse outcome. In short, while the relationship between pattern of ventricular dimensions and survival remains contentious, that reduced inotropy occurs in septic shock is certain.

The poor myocardial performance in septic shock is not purely due to contractility failure alone. Slower left ventricular filling and aberrant left ventricular relaxation, signifying diastolic dysfunction, have been observed in septic patients.[8-10] Similarly, the myocardial depression is not restricted to left ventricle. Decreased right ventricular ejection fraction (RVEF) and right ventricular dilation have been documented.[11-13] Meanwhile, the evidence of right ventricular dysfunction in septic shock calls for a cautious interpretation of central venous pressure (CVP). Schneider and colleagues[12] identified a subgroup of patients who failed to show an increase

in the right ventricular volume index (RVEDVI) in response to volume loading, despite a rise in CVP.

As the above manifestations mimic cardiac failure from ischaemia or infarction, the initial theory for the myocardial depression in sepsis naturally evolved around the concept of myocardial hypoperfusion. Serial measurements of coronary blood flow in septic patients, using thermodilution coronary sinus catheters, however revealed normal or elevated flow compared with normal controls.[14] There was also no difference in blood flow between those who developed myocardial depression and those who did not. Nevertheless, microvascular thrombosis and subsequent myocardial microinfarction, which causes no significant difference in coronary flow, remains a potential cause for myocardial injury.[15] This is supported by the close relationship between inflammatory cytokines and a procoagulant state seen in severe sepsis.[16]

At the cellular levels, myocardial dysfunction appears to play a central role in the myocardial depression of septic shock.[17] This is related to ATP depletion, antioxidant depletion and nitric oxide overproduction.[18] Various cytokines are involved in these inflammatory activities, with tumor necrosis factor (TNF) and interleukin-1 (IL-1) believed to be the predominant mediators.[19,20]

HAEMODYNAMIC MONITORING AND THE USE OF BIOMARKERS

That optimization of fluid therapy is key to septic shock management cannot be emphasized enough. Unfortunately, the most reliable monitor to its assessment is still arguable. CVP, perhaps the most commonly used, has long been shown to be a poor estimate of left ventricular preload in sepsis.[21] Pulmonary artery catheter (PAC), on the other hand, allows a better estimate through its pulmonary artery occlusion pressure (PAOP). Other parameters available from PAC like the cardiac index (CI) and the systemic vascular resistance index (SVRI) also offer better insight into cardiovascular dysfunction in septic shock. Nevertheless, recent evidence highlighting no proven survival benefit with PAC[22] and in fact a higher risk of morbidity,[23] has resulted in a significant drop in its use.

Echocardiography, transoesophageal (TOE) in particular, permits comprehensive study of both systolic and diastolic dysfunction and gives a reliable assessment of the myocardial depression in septic shock. The drawbacks of TOE are however the high degree of training it requires, the issues with its availability as well as its inability to provide continuous monitoring in intensive care setting.

The limitations of these bedside monitors trigger the interest on the role of biomarkers in detecting myocardial dysfunction in sepsis. Cardiac troponins and B-type natriuretic peptides (BNP), introduced for diagnosis of acute coronary syndrome and congestive heart failure respectively, are two biomarkers that have been extensively studied.

Many studies reported a relationship between elevated cardiac troponin I (cTnI) or cardiac troponin T (cTnT) and left ventricular dysfunction in sepsis.[24-27] It was also demonstrated that apart from indicating presence of myocardial depression, the elevated troponin levels also indicated a higher severity of the disease and a worse prognosis.[25,27]

The exact mechanisms for the troponin release in sepsis are still unclear as the coronary blood flow is either normal or elevated in sepsis.[14] This suggests the presence of mechanisms other than thrombotic coronary artery occlusion, probably a transient loss in membrane integrity with subsequent troponin leakage or microvascular thrombotic injury.[28] It is also inconclusive whether the troponin release in sepsis reflects irreversible myocardial damage or reversible myocardial depression.[29]

Based on the uniform results of studies looking at cardiac troponins and myocardial dysfunction in sepsis, it is recommended that cardiac troponins be integrated into haemodynamic monitoring of severe sepsis or septic shock. It may help to identify patients requiring early and aggressive supportive therapy.[15] One consideration in septic shock patients, however, will be the relatively higher incidence of renal failure. Cardiac troponins, especially cTnT, are excreted mainly by the kidney[30] and have been shown to be of low specificity for assessment of acute coronary syndrome in end-stage renal failure patients.[30-32] Elevated troponin levels in septic patients with renal failure will thus warrant cautious interpretation.[15]

The other biomarker, BNP, is a hormone of which synthesis and release is stimulated by myocyte stretch.[33] Maisel and colleagues[34] showed that BNP was useful in distinguishing dyspnoea caused by congestive heart failure from noncardiac dyspnoea in an emergency setting. When examined in severe sepsis, however, the relationship between BNP and the left-sided filling pressures was shown to be weak.[35-37] As such, the use of BNP for detection of myocardial dysfunction is discouraged at the moment.[15]

MANAGEMENT

Early goal directed therapy (EGDT) study by Rivers and colleagues[4] is seen by many as a landmark study in the treatment of severe sepsis and septic shock. What appeals people to it is perhaps the message that it advocates: simple treatments done early and done well can have a significant impact in reducing mortality. In EGDT, strong consideration is given towards myocardial dysfunction in septic shock. An important feature of EGDT with regard to myocardial dysfunction is the emphasis on early optimization of preload and oxygen delivery by haemoglobin optimization before the inotropic therapy. The early intervention, within hours of presentation, has been attributed as the main difference between EGDT and previous haemodynamic optimization trials[38] by Shoemaker and colleagues,[39] Hayes and colleagues[40] and Gattinoni and colleagues.[41] Adequate preload on the other hand, will optimize benefit from dobutamine therapy and has been shown to improve outcome of high risk surgical patients when titrated in a goal directed manner.[42] Hypotension that develops after initiation of dobutamine may actually suggest unrecognized hypovolaemia.

A survey of sepsis initiatives in 12 centres that included EGDT in their programs revealed a significant improvement in mean mortality rate from 44.8 ± 7.8% in the pre-implementation period to 24.5 ± 5.5% post-implementation. Although many of the studies in the survey were retrospective case-control studies, they highlight the fact that rapid interventions, often not provided until ICU admission, uniformly improves patient outcome.[37] In essence, septic shock, with or without myocardial depression, needs to be intervened early and well.

With respect to the choice of inotropic agent in myocardial depression in sepsis, there are emerging data that support the use of levosimendan, a novel calcium sensitizer and K-ATP channel opener. Morelli and colleagues[43] demonstrated that in sepsis-induced cardiac dysfunction persisting after 48 hours of conventional treatment that included dobutamine, levosimendan improved both systemic haemodynamics and regional perfusion. This was reflected in improved LVEF, decreased LVEDV and increased gastric mucosal flow, creatinine clearance, urinary output, accompanied with decreased lactate concentrations. Similar improvements were seen in a case series of six patients with refractory septic shock, despite conventional resuscitation.[44] A relatively new drug, more evidence on its role in septic myocardial depression is expected in the near future.

CONCLUSION

Septic shock continues to be a major contributing factor to ICU mortality. A thorough understanding of its manifestations including myocardial depression, will go a long way in improving its outcome. While there are new approaches in dealing with myocardial depression, like the use of cardiac troponins to stratify patients and the introduction of the novel drug levosimendan; basic, goal-directed measures done early and done well should remain the mainstay of treatment.

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Intensive Insulin Therapy In The ICU – Where Are We?

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INTRODUCTION

It is well known that any type of acute illness or injury results in insulin resistance, glucose intolerance and hyperglycemia, a constellation termed "diabetes of injury" even when glucose homeostasis has previously been normal. This diabetes of injury has been interpreted as an adaptive stress response promoting cellular glucose uptake in non-insulin-dependent tissues e.g. the nervous system and the blood cells and as such important for survival.

However, the association of hyperglycaemia and adverse clinical outcomes has been shown in a number of clinical situations: myocardial infarction and acute coronary syndromes,[1,2] stroke,[3-5] postoperative wound infections,[6-8] and trauma.[9,10] A randomized study in patients with acute myocardial infarction found that implementation of strict euglycemia with insulin infusions for 24 hours followed by multiple daily insulin injections caused a prompt and sustained improvement in all-cause mortality.[11] In addition, two prospective studies showed that tight glycemic control improved outcome and reduced infectious complications of cardiac surgery.[12,13]

The role of tight glycemic control in the critically ill patients seemed to be answered by a paper entitled "Intensive insulin therapy in critically ill patients"[14] published in the New England Journal of Medicine.

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

The paper describes a prospective randomized controlled study carried out by Van den Berghe and colleagues in the surgical intensive care unit (ICU) in the Catholic University of Leuven in Belgium. In this study, all adults receiving mechanical ventilation were randomized to receive either intensive insulin therapy (insulin started if blood glucose > 6.1mmol/L with target blood glucose 4.4 to 6.1 mmol/L) or conventional insulin therapy (with insulin started if blood glucose > 11.9 mmol/L with target blood glucose 10 to 11.1 mmol/L). The initial plan was to enroll 2500 patients in order to detect an absolute difference in mortality between the 2 groups of 5% among patients who stayed in ICU for more than 5 days and of 2% among all patients in ICU. The fourth interim analysis indicated that conventional treatment was inferior and the study was stopped. Finally a total of 1548 patients were enrolled.

Intensive insulin therapy (maintenance of blood glucose at a level between 4.4 to 6.1 mmol/L) reduced overall ICU mortality from 8.0 per cent with conventional treatment (maintenance of blood glucose at a level between 10.0 to 11.1 mmol/L) to 4.6 per cent ($p = 0.005$). This effect was primarily due to reduced ICU mortality in patients admitted longer than 5 days (10.6 versus 20.2% $p = 0.007$). The in-hospital mortality was also lower in the intensive insulin therapy group (7.2 versus 10.9%, $p = 0.01$). Intensive insulin therapy also reduced bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red cell transfusions by 50%, and critical illness polyneuropathy by 44%.

As expected, 98.7% of the patients in the intensive treatment group received IV insulin, compared with 39% in the conventional treatment group. However episodes of hypoglycaemia (blood glucose < 2.2 mmol/L) were more common in the intensive insulin therapy group (5.0 versus 0.7%).

The results are impressive. As this is a large sample randomized controlled trial (level 2 evidence),

theoretically the results should be credible. The investigators of the study in a later analysis[15] showed that metabolic control, as reflected by normoglycemia, rather than the infused insulin dose per se, statistically explained the observed protective effects of intensive insulin therapy on outcome of critical illness. The chief investigator also in a subsequent article[16] attempted to explain the mechanisms likely to be responsible for the acute life-saving effects of intensive insulin therapy in the ICU. She pointed out that it was likely that there was accelerated glucose toxicity (via cellular glucose overload and more pronounced toxic side effects of oxidative phosphorylation) in the critically ill and preventing this glucose toxicity played a crucial role in the beneficial effects of intensive insulin therapy.

In addition, subsequent publications of high quality observational studies[17-19] supported the finding that tight glycemic control seemed to be the way to go; a target glucose value < 7.7 mmol/L, as opposed to 6.1 mmol/L, might optimize survival and decrease the risk of iatrogenic hypoglycemia.

The 3 observational studies are:

1. Krinsley J S[17] conducted a retrospective review of glucose values of 1826 consecutive patients admitted to a medical/surgical ICU at the Stamford Hospital between Oct 1, 1999 and April 4, 2002. He found that the lowest hospital mortality i.e. 9.6%, occurred among patients with mean glucose values between 4.4 and 5.5 mmol/L and hospital mortality increased progressively as glucose values increased, reaching 42.5% among patients with mean glucose values > 16.6 mmol/L
2. Finney SJ et al[18] carried out a single-center, prospective observational study of 531 patients admitted over the first 6 months of 2002 to an adult ICU in a UK national referral center for cardio-respiratory surgery and medicine. In this study, regression models suggested that a mortality benefit existed when the blood glucose was maintained below a threshold of 8.1 mmol/L. The degree of mortality benefit appeared directly related to the stringency of blood glucose control.
3. Krinsley J S[19] in a retrospective, single-center, unblinded, before-and-after trial study compared the outcomes of 800 patients admitted consecutively to the ICU immediately before institution of the glucose management protocol (February 23, 2002, through January 31, 2003) to those of the first 800 patients (February 1, 2003, through January 10, 2004) admitted after institution of the protocol to maintain blood glucose levels lower than 7.8 mmol/L. He found that institution of the intensive insulin protocol reduced hospital mortality by 29.3% ($p = 0.02$), ICU length of stay by 10.8% ($p = 0.01$), mean glucose level (from 8.5 to 7.3 mmol/L with $p < 0.001$), new renal insufficiency by 75% ($p = 0.03$) and transfusion of RBC by 18.7% ($p = 0.04$) among a heterogenous population of critically ill adult patients.

Tight glucose control, albeit at a higher level (< 8.3 mmol/L) in a severely septic patient has been advocated as part of the Surviving Sepsis Campaign guidelines.[20]

CRITICISMS OF INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

However critics of the Leuven study on intensive insulin therapy in the surgical intensive care unit[14] question the validity of the study. The limitations or concerns[21-25] are:

1. It was not blinded (though the investigators could hardly be blinded), which raises the possibility of both conscious and unconscious bias.
2. Most patients were recruited after surgery (about 63% from cardiac surgery) from a single center.
3. Recruited patients received intravenous glucose on arrival at the ICU at 200 to 300 g /day (the equivalent of 2-3 L of 10% glucose per day), an unusual practice among most ICUs.
4. This regimen was followed by the initiation of total parenteral nutrition, or enteral feeding, or combined feeding for all patients (presumably including cardiac surgery patients) within 24 hours, also an unusual practice.
5. The mortality of the cardiac surgery patients in the conventional treatment group was 5.1%, double the national average in Australia and 5 times that in a hospital where one of the authors (R.B.) works.[26]

6. The mortality in relation to the severity of illness (median APACHE score was 9 for both groups) among patients in the conventional group was relatively high.
7. The relative reduction in mortality was extremely high: 34% for a decrease of only 2.8 mmol/L in morning glucose levels.
8. The risk of hypoglycaemia with its potential morbidity was 5.0% in the intensive insulin therapy group compared to 0.7% in the conventional treatment group.

Indeed a strong critique[21] of the Van den Berghe study suggested that a more reasonable conclusion for that study might have been that administration of excessive intravenous glucose without strong attempts to control its consequences increases mortality in critically ill surgical patients.

The critiques may be right in their argument as a subsequent study by the same group of investigators in 2006 did not show results as impressive as the initial randomized controlled trial (RCT) paper on intensive insulin therapy in 2001.

INTENSIVE INSULIN THERAPY IN THE MEDICAL ICU

As the first study on intensive insulin therapy in 2001 was carried out primarily in the surgical ICU, the same authors proceeded to repeat the study in the medical ICU.[27] The initial plan was to enroll 1200 patients who were considered to need intensive care for at least three days in order to detect an absolute reduction in the risk of death of 7% after at least 3 days of intensive insulin therapy.

The result failed to show any decrease in mortality (40.0% in the conventional-treatment group versus 37.3% in the intensive-treatment group, p = 0.33) though there was a significant reduction in morbidity by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.

The most surprising part of the study was the analysis of the subset of patients who stayed in the ICU for less than three days. Among 433 patients who stayed in the ICU for less than three days, mortality was greater in the intensive insulin therapy group. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 patients who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (p = 0.009) and in addition to a significant reduction in newly acquired kidney injury, earlier weaning from mechanical ventilation, earlier discharge from ICU and hospital, a further significant reduction in hyperbilirubinemia and hyperinflammation was observed.

It is important to note that 98% of the patients in the intensive treatment group received IV insulin, compared with 70% in the conventional treatment group. Episodes of hypoglycemia (glucose < 2.2 mmol/L) were much more common in the intensive treatment group (18.7 versus 3.1%).

COMPARISONS AND CONCLUSIONS FROM THE 2 INTENSIVE INSULIN THERAPY RCTS

Both trials were prospective, randomized, controlled study of adequate power. The main limitations were lack of blinding and single center. However, the initial trial in the surgical ICU was stopped early and therefore runs a risk of an exaggeration of positive results[28,29] while the second trial runs a risk of over-emphasizing post hoc result and secondary end points.[28]

Therefore these 2 large sample RCTs in a single center would suggest that:

1. Initial intensive insulin therapy study done on surgical patients (2001) cannot be extrapolated to medical ICU patients. There is in fact an increase in mortality in the first 3 days of ICU stay for the medical patients. Could the increase in mortality be a result of hypoglycemia because of the intensive insulin therapy?
2. The benefit of intensive insulin therapy is seen in patients who stay longer in ICU, 5 days for the surgical patients and 3 days for the medical patients. The primary endpoint is a reduction in ICU mortality.
3. The secondary endpoints i.e. reduction in hospital mortality, reduction in acute kidney injury, reduction in the duration of mechanical

ventilation and reduction in the length of ICU and hospital stay hold true for both surgical and medical patients.

Two additional multi-center RCTs of intensive insulin therapy, one focusing on patients with severe sepsis[30] and the other on medical and surgical ICU patients[31] have been carried out but failed to show reduction in mortality.

THE VISEP STUDY

The VISEP (Efficacy of volume substitution and insulin therapy in severe sepsis) trial has just been published in the New England Journal of Medicine in January 2008.[30] It is a prospective randomized multi-center study comparing intensive insulin therapy with conventional insulin therapy and 10% pentastarch, a low molecular weight hydroxyethyl starch (HES 200/0.5) with Ringer's lactate as volume resuscitation, in patients with severe sepsis and septic shock, using a two-by-two factorial, open-label design. The co-primary end-points were 28 day mortality from any cause and morbidity as measured by the mean score on the Sequential Organ Failure Assessment (SOFA).

All adult patients (in multidisciplinary ICUs at 18 tertiary hospitals in Germany) with severe sepsis or septic shock who met the criteria for enrollment were randomized to receive either intensive insulin therapy (insulin started if blood glucose > 6.1mmol/L with target blood glucose 4.4 to 6.1 mmol/L) or conventional insulin therapy (with insulin started if blood glucose > 11.1 mmol/L with target blood glucose 10 to 11.1 mmol/L). The insulin dose was adjusted according to the Leuven titration guidelines[15] which were used in their 2 studies.[14,27] This trial which started in April 2003 was designed to randomize 600 patients in the first stage of adaptive study design to detect a difference of 1.2 in the mean SOFA score or a reduction in mortality from 40% to 30% at 28 days.

After the first safety analysis involving 488 patients, the intensive insulin therapy was terminated early owing to an increase in the incidence of hypoglycemia in the intensive insulin therapy arm (12.1% versus 2.1%, $p < 0.001$). The comparison between HES and Ringer's lactate was continued with all patients receiving conventional insulin therapy. As fluid resuscitation is not point of discussion here, the reader may refer to the original paper for details.

Among the 537 patients who could be evaluated, there was no significant difference in any of the primary and secondary end-points between the intensive therapy group and the conventional therapy group, namely 28 day mortality (24.7% versus 26.0%, $p = 0.74$), mean SOFA scores (7.8 versus 7.7 points, $p = 0.88$), the development of acute renal failure (31.1% versus 26.6%, $p = 0.25$), the need for renal replacement therapy (27.5% versus 22.5%, $p = 0.19$), the median number of red cell transfusion, the use of vasopressors and the duration of mechanical ventilation.

It is important to note that analyses of interaction did not show any significant interactions between the two study interventions with respect to 28 day mortality. In addition, subgroup analyses regarding length of ICU stay and resolution of organ injury and exploratory analyses that stratified data according to the mean morning blood glucose level also did not show any significant differences between the two study groups.

THE GLUCONTROL STUDY

The GluControl (Glucontrol study: comparing the effects of two glucose control regimens by insulin in intensive care unit patients) study[31] is a prospective, randomized, controlled, multi-center study. The study aimed to compare the effects of two regimens of insulin therapy, respectively titrated to achieve a blood sugar level between 4.4 and 6.1 mmol/L (80 and 110 mg/dl, respectively) and between 7.8 and 10.0 mmol/L (140 and 180 mg/dl, respectively) with regards to mortality and morbidity in a mixed population of critically ill patients (3500 patients).

The study which started in November 2004 was stopped after recruiting 1101 patients due to high incidence of severe hypoglycaemia in the intensive insulin therapy patients (8.6% versus 2.4% in the conventional insulin therapy patients, $p<0.001$).

There was no difference in mortality or length of stay between the 2 groups.

CONCLUSIONS FROM THE 4 RANDOMIZED CONTROLLED STUDIES

The best available evidence suggests that intensive insulin therapy may be an important treatment modality in critically ill *surgical* patients especially those who have undergone cardiac surgery. (Grade of recommendation: A)

However whether intensive insulin therapy can be applied to heterogenous medical ICU populations would remain controversial. The VISEP study and the medical ICU study by Van den Berghe et al established that intensive insulin therapy does not produce consistent benefits in critically ill *medical* patients but increases the risk of hypoglycemic episodes.

In summary, in the era of evidence-based medicine, these 4 randomized controlled trials do not give us conclusive evidence on whether tight glucose control should be the standard of care in the management of critically ill patients and if it is to be the standard of care, what should the target glucose level be as the risk of hypoglycemia is real.

Fortunately, a large prospective, multi-center study is now well underway, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study.[32] The NICE-SUGAR study is a multi-centre, open label, randomized controlled trial of blood glucose management with an intensive insulin regimen to maintain blood glucose between 4.5 – 6.0 mmol/L versus an insulin regimen maintaining blood glucose less than 10.0 mmol/L with insulin being infused if blood glucose exceeds 10.0 mmol/L, and adjusted when needed to maintain blood glucose between 8.0 – 10.0 mmol/L. The primary aim of the study is to compare the effects of the two blood glucose targets on 90 day all-cause mortality in intensive care patients who are predicted on admission to stay in the ICU for at least one full calendar day. The study aims to enroll a total of 5000 patients; 4500 patients to be recruited in Australia and New Zealand and 500 in Canada. This study started in April 2005.

In August 2006, the study data and safety monitoring board reviewed the interim results of the first 2000 patients, determining that the study should continue and that there was no reason for the interim analysis to be unblinded. In other words it is safe to proceed with the study. An additional interim analysis is scheduled to be carried out when follow-up of 4,000 patients is completed which is estimated to be the end of 2007. The results of the analysis are not released yet and will be much awaited.

What should we do in the interim period while waiting for the results of this robust study?

We must carefully consider the potential risks and benefits when implementing intensive insulin therapy in the medical ICU. As Drs Angus and Abraham[24] suggested in the year 2005 – " …It may be valuable to remember that, although the evidence for tight glycemic control does not yet support a grade A recommendation, it does appear to be stronger than that for continuing our existing practice of tolerating hyperglycemia. Thus, we should probably explore ways to introduce some form of tight glucose control during this interim period that seems feasible and safe given local considerations. Once better evidence is available, we can modify our plans accordingly." If we introduce some form of tight glucose control, we should keep the glucose level higher such as between 6 – 8 mmol/L rather than 4 – 6 mmol/L to avoid hypoglycaemia.

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