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Evidence-based Medicine – an everyday practice

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Introduction

Evidence-based medicine (EBM) has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients". However the "current best evidence" in intensive care medicine is seldom from randomised controlled trials (RCTs) leaving intensivists with only lesser quality evidence to guide clinical care in circumstances of considerable uncertainty and patient-risk.

Method

Articles concerning EBM in intensive care were sought from a Medline and non-Medline search of relevant English literature and then extracted and analysed and supplemented by personal experience.

Results

Publication of randomised controlled trials in intensive care medicine was sporadic until 1989, has increased dramatically since and is currently running at around 3 trials per week. Most of these trials have involved small numbers of patients and compared two pharmacologic treatments using surrogate endpoints. More recently, large multi-centre studies have been conducted examining both medications and therapeutic strategies with mortality endpoints. Most have shown equivalence but some have shown harm – enabling future patients to avoid these therapies. Very few have shown benefit of one treatment or strategy over the control condition. Evidence-based guidelines for some common conditions (e.g. traumatic brain injury) have been produced by consortia but these guidelines are often more guided by prospective cohort studies (e.g. the Traumatic Coma Data Bank) than by RCT evidence. Studies examining conformance to such guidelines have usually shown poor compliance and studies of strategies to improve compliance are (so far) rare. In our own practice, a consensual model of group decision-making, with a commitment to both "best available evidence" and cost-effective treatment has resulted in reduced resource use, improved outcomes and consistency of evidence-based practice.

Conclusion

EBM in intensive care medicine is undergoing rapid acceptance as a desirable practice style and is increasingly supported by level I (RCT) evidence, albeit much of it showing only lack of benefit for innovations. Evidence-based strategies to improve compliance with evidence-based guidelines are urgently needed but a consensual model of intensivist group practice can facilitate such compliance.

Large hemispheric infarcts: are there any good options?

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Complete middle cerebral artery (MCA) territory infarctions that progress to coma, respiratory failure and admission to the ICU, has been termed malignant MCA infarcts by Hacke et al in 1996. The mortality rate from this condition is widely reported as 55-80%. While patients are typically alert on presentation, they progress to coma in 1-3 days and eventual brain death in 2-5 days. This deterioration is the result of progressive brain swelling causing intracranial hypertension and brain herniation.

Attempts to lower high intracranial pressures (ICP) in malignant MCA infarcts with hyperventilation, mannitol, barbiturate coma and drainage of CSF have not resulted in improved outcomes or lower mortalities. These treatment modalities usually end up shrinking the normal hemisphere more, worsening the brain herniation.

Decompressive craniectomy (DC) involves removing a segment of the cranial vault together with a duroplasty to allow expansion of edematous tissue away from the lateral ventricle, diencephalons and brain stem. This reduces ICP, preserves cerebral blood flow and helps to protect the surrounding brain tissues from secondary injuries. In a prospective, non-randomized trial, Rieke et al reported mortality of 34% in the DC group vs 76% in the conservative management group. They also reported better functional outcomes among survivors in the DC group. The benefits from DC are reportedly greater among younger patients and when surgery is performed early after symptom onset.

Hypothermia, with a core temperature of 33ºC has also been reported to lower mortality following large MCA infarcts. When compared with DC in a non-randomized trial, Georgiadis et al found that patients in the moderate hypothermia group had a higher mortality compared to the DC group (47% vs 12%).

Oxygen: the more the better

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Hyperbaric Oxygen Therapy (HBOT) is the intermittent administration of 100% oxygen at pressures greater than atmospheric pressure and is done in either monoplace or multiplace hyperbaric chambers. Indications for HBOT include the following:

1. Air or gas embolism
2. Carbon monoxide poisoning
3. Clostridial myositis and myonecrosis
4. Crush injury, compartment syndrome and acute traumatic ischemias
5. Decompression illness
6. Enhancement of healing in selected problem wound
7. Exceptional blood loss (anaemia)
8. Intracranial abscess
9. Necrotising soft tissue infections
10. Osteomyelitis (refractory)
11. Delayed radiation injury
12. Compromised skin grafts and flaps
13. Thermal burns

Several of these conditions may present as critically ill patients in the intensive care and would require HBOT as adjunctive treatment for an improved outcome – examples of these include gas gangrene, necrotising fasciitis, and acute traumatic ischemias. The provision of critical care in the hyperbaric chamber presents unique challenges to the intensivist and these include the effects of pressure (Boyle's Law) on the patient, equipment and the medical attendant. Similar to the anaesthetist's role in assessing fitness for an operation, the hyperbaric physician needs to determine the fitness for treatment. Treatments are not without potential risks (central nervous system and pulmonary oxygen toxicity, barotrauma) and these have to be weighed against the benefit for the patient – a pre-treatment consultation between the primary physician, intensivist and the hyperbaric physician is essential.

Extracorporeal oxygen - the best

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Extracorporeal techniques in the form of cardiopulmonary bypass function primarily as temporary haemodynamic support during heart surgery. The circuit, in essence, involves drainage of deoxygenated blood from the right atrium to a venous reservoir, via a pump through an oxygenator and heat exchanger, through a filter and back to the aorta. With modifications of this circuit, extracorporeal membrane oxygenation (ECMO) can be established to achieve gas exchange with or without cardiac support for a longer period of time.

ECMO can be established in 2 forms: veno-venous, primarily for respiratory failure or veno-arterial circuit for circulatory failure.

With a patient on ECMO, ventilator settings can be set to "lung rest", this facilitates lung repair and avoids the baro- or volutrauma of the mechanical ventilator. The technique has been refined in neonates and children, in whom survival rates are consistently high. ECMO usually applied to adults with respiratory failure when the mortality risk exceeds 80%. Even with these ill patients, the survival rate can be up to 50% in experienced centres.

ECMO is effective and safe in keeping alive patients with severe respiratory failure. In addition to direct and indirect treatment of the lungs during ECMO, the technique allows time for treatment of other conditions and other organ failure. By stabilizing haemodynamics, ECMO also allows transfer of patients to a tertiary centre for further management.

Inhaled nitric oxide therapy for newborn infants with hypoxic respiratory failure

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Nitric oxide is an important modulator of vascular tone in the pulmonary circulation and regulates smooth muscle tone via changes in cyclic guanosine monophosphate. Exogenous inhaled nitric oxide (INO) diffuses from alveoli to pulmonary smooth muscle and produces vasodilatation by the same mechanism as endothelial-derived NO. Excess NO diffuses into the blood stream where it is rapidly inactivated by binding to haemoglobin and subsequent metabolism to nitrates and nitrites. INO is a selective pulmonary vasodilator and does not cause systemic hypotension. Initial studies used higher concentrations (40 – 80 ppm) of INO. Randomised controlled trials have shown lower doses (5 ppm) were equally effective as higher doses (20 ppm). Initial treatment with a subtherapeutic dose of INO may diminish the clinical response to higher doses. In newborn infants INO has a role in the management of persistent pulmonary hypertension of the newborn with or without lung disease, hypoxic respiratory failure and pulmonary hypertensive crisis in post-cardiac surgical patients. Meta-analysis of the results of 8 randomised trials in term or near-term infants demonstrated that INO improved oxygenation and reduced the combined outcome of need for ECMO or death. Combined intervention of INO and high frequency oscillatory ventilation is more successful than either therapy alone in rescuing infants with respiratory failure. There are numerous reports of INO improving oxygenation in preterm infants but randomized trials have not clearly demonstrated significant benefits. Adverse effects viz high NO_2 levels resulting in pulmonary toxicity and methemoglobinaemia are reported with high doses and are not important problems in the NICU.

Monitoring regional circulation

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As the aim of cardiovascular support is to ensure adequate oxygen delivery to tissues it makes intuitive sense to monitor regional circulation. There are devices available to monitor brain, skeletal muscle, skin, splanchnic and lingual circulations. It is not, however, possible to monitor all regional circulations, which raises the question of which circulation should be monitored.

Ideally the regional circulation that is monitored should have the following characteristics:

- It should be particularly sensitive to decreases in global oxygen delivery such that the presence of adequate blood flow to that region makes inadequate blood flow in other regions unlikely.
- The organ(s) supplied by that circulation should be of major importance either because their function cannot be easily replaced or because dysfunction of that organ has major impact on the function of other organs.

On this basis monitoring of the splanchnic circulation using gastric tonometry received great interest in the 1990s. Low gastric intramucosal pH was found be associated with worse outcome in many studies leading to the hope that treatment titrated against intramucosal pH might reduce mortality. Although early data suggested that this might be the case other investigators were subsequently unable to confirm this finding. Subsequently it was suggested that intramucosal PCO_2 might be a more specific measure of splanchnic perfusion, particularly if the difference between intramucosal and arterial PCO_2 was monitored. Despite the theoretical advantages of this parameter over intramucosal pH it has not been widely adopted.

Monitoring of the lingual circulation has been suggested as an alternative to gastric tonometry. There are data suggesting that it is a moderately sensitive and specific predictor of outcome in critically ill patients and it has the advantage that the sublingual area is easily accessible. However, there is no data to show this circulation is particularly prone to ischaemia or any intrinsic reason to believe that should be. Furthermore the tongue failure is of little consequence in the critically ill patient.

Animal data suggest that monitoring the subcutaneous oxygen tension may be as sensitive method of detecting covert shock as monitoring the splanchnic circulation but the data are limited and human data are lacking.

Management of post-operative atrial fibrillation

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Atrial fibrillation is a common arrhythmia in post operative states. In open heart surgery, the incidence is as high as 20 – 50%.

While it is not immediately life-threatening, the onset of atrial fibrillation, especially if accompanied by rapid ventricular response, can cause hypotension, heart failure and worsening of angina. This is especially so in the elderly and those with impaired ventricular function.

Pre-operative co-morbid conditions predispose to the development of atrial fibrillation post operatively. These include poor ventricular function, a previous history of atrial fibrillation, chronic obstructive lung disease and hyperthyroidism. Post operative conditions aggravate the likelihood of atrial fibrillation, such as hypokalaemia, hypoxaemia, anemia, hypomagnesaemia, myocardial ischemia, pulmonary embolism and the use of sympathomimetic amines for pressor support.

Atrial fibrillation which causes severe haemodynamic compromise should be cardioverted immediately (electrical cardioversion).

However post operative atrial fibrillation is often recurrent and may be persistent and therefore the use of rate slowing agents such as beta blockers, calcium channel blockers and digoxin may be necessary in these situations. Exercise caution in those with poor ventricular function when using intravenous beta blockers or calcium channel blockers. Intravenous amiodarone is often

used for rate control in patients with hypotension or heart failure and is quite well tolerated but should be given through a central vein as it causes severe phlebitis.

When AF is likely to be recurrent, especially after open heart surgery, oral amiodarone or sotalol is often used to help maintain sinus rhythm in the first month. Class Ic agents such as flecainide and propafenone are contraindicated in those with uncorrected ischemia and/or poor ventricular function. If AF persists for more than 48 hours, anticoagulation should be considered to reduce thromboembolic complications. Reversible factors such as hypoxaemia, hypokalaemia, hypomagnesaemia should be corrected.

Haemoptysis: ICU management

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Haemoptysis is defined as expectoration of blood from below larynx. Haemoptysis must be differentiated from haematemesis. It contributes 6.8% of outpatient pulmonary clinic visits, 11% of admissions to a hospital pulmonary service and 38% of patients referred to a thoracic surgery practice. About 4.8% to 14% of haemoptysis is massive.

Massive haemoptysis has been defined by various authors using different criteria:
1. "Volume" definition: > 100 to ≥ 600 mL/24 hr, or ≥ 400 mL in 6 hr.
2. "Magnitude of effect" definition: causes death, requires hospitalization, evidence of systemic blood loss, requires plasma or blood transfusion (threatens life by blood loss ≥ 1000 mL total or ≥ 150 mL/hr), risk of large aspiration/airway obstruction.

Common causes of massive haemoptysis are TB (rupture of Rasmussen's aneurysm), bronchiectasis (erosion of bronchial vasculature), bronchogenic carcinoma (invasion of pulmonary vessels), lung abscess (destruction of fairly normal vessels due to inflammation), aspergilloma, bronchovascular and AV fistulas, trauma, pulmonary renal syndrome, and among the white persons, cystic fibrosis.

Role of bronchoscopy

Active bleeding and site of bleeding are visualized more commonly with early bronchoscopy (within 48 hr) than with more delayed examination. Earlier bronchoscopy in non-massive haemoptysis only infrequently alters the overall patient management.

Flexible bronchoscope gives better visualization and access to distal airways. Rigid bronchoscope allows better suctioning and airway control in massive haemoptysis. Flexible bronchoscope can be passed through the rigid bronchoscope. Acute control of bleeding can sometimes be achieved with instruments and catheters placed through bronchoscope or by instillation of pharmacologic agents.

ICU management

Massive haemoptysis can lead to asphyxiation, airway obstruction, shock and exsanguination. Principles in ICU management of massive haemoptysis are:
1. Airway protection and adequate oxygenation
2. Patient haemodynamic stabilization
3. Suppress cough
4. Localize source of bleeding
5. Control bleeding site
6. Administer specific therapy

Airway protection and adequate oxygenation

Anatomical dead space of major airways is 100-200 mL. Death from asphyxiation in massive haemoptysis can result from as little as 150 mL of blood filling the airways. Life saving measures include:

1. Position with bleeding lung down (lateral decubitus)
2. Supplemental oxygen
3. Endotracheal intubation (single- or double lumen [Carlen's tube]) when airway is compromised or there is continuing active bleeding. A double lumen ETT permits isolation of normal lung and minimize aspiration risk while allowing selective ventilation.

Control bleeding site

1. Bronchoscopic procedures: bronchial packing through a rigid bronchoscope, tamponade of airway with a balloon tipped (Fogarty) catheter, bronchial lavage with cold saline, topical epinephrine (1:20,000), thrombin, thrombin-fibrinogen, Nd-YAG laser coagulation of visible endobronchial lesions.
2. Bronchial artery embolization (BAE) has become the first line treatment for massive or recurrent haemoptysis in both acute and chronic settings. BAE has high success rate of 64% to 100% in immediate control. Repeat embolization can be performed safely in recurrent haemoptysis. BAE may help to avoid surgery in patients who are not good surgical candidates. It is important to treat underlying pulmonary process to decrease vascularity and development of vascular collaterals.
3. Surgical resection: serious bleeding not controlled by other means, localized disease, catheter related pulmonary artery rupture, mycetoma with profuse collateral arterial supply, BAE unavailable or technically impossible.
4. Correct coagulopathy: FFP, vitamin K, platelets.

Overall mortality of massive haemoptysis is 7%. Poor prognostic factors are bleeding > 1000 mL/24 hr, radiographic evidence of aspiration, haemodynamic instability, haemoptysis caused by neoplasm, inadequate pulmonary function, debilitated states, bilateral pulmonary bleeding sources, inability to localize source of bleeding and metastatic cancer.

ICU triage: its effect on outcome

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Triage is the process of selecting patients according to priority, in a situation where resources are insufficient to meet the demand. In general this process is designed to prioritize those who will derive the greatest benefit from the resource. Thus patients who will die despite Intensive Care should, in general, not be admitted. Equally those who will survive anyway, without Intensive Care, should not be admitted either. Those who should be admitted are those for whom Intensive Care has a significant potential to alter outcome. Whether this process of triage has any effect on outcome depends on whether Intensive Care actually alters outcome or not. If it does, then admission of a greater proportion of those referred for admission will result in a lower mortality for the referred group as a whole. The available data suggest that Intensive Care does reduce mortality and thus the necessity to triage admissions to ICU is likely to be leading to unnecessary deaths.

A second question is whether apparent ICU performance is altered by triage. In other words whether by selecting particular patients that are expected to derive a greater benefit from ICU one alters the case-mix adjusted mortality. Triage data suggest that there is the potential for triage patterns to impact on standardized mortality ratios but a study of different levels of triage at different time periods in our ICU suggest that any such effect is likely to be small.

End-of-life: when to stop?

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Introduction

Intensivists often treat patients with catastrophic illness and withdraw therapies when subsequent progress is poor.

Method

Literature pertaining to prediction of poor outcome, consequences of poor outcomes, processes of decision-making under conditions of uncertainty and recommended clinical practice for withdrawal of treatment was reviewed. How intensive therapies were withdrawn in our clinical practice is described in four cohorts of patients with severe sepsis, severe traumatic brain injury (TBI), post-resuscitation from cardiac arrest and subarachnoid haemorrhage.

Results

Features highly predictive of poor outcome are well quantified for septic multiple organ failure, severe TBI and hypoxic-ischaemic encephalopathy and have recently been described for stroke. Decision-making in everyday life involves consideration of the risk of unacceptably bad outcome along with the probability of acceptably good outcome. "Framing" information can influence decision-making to promote or reduce risk-aversion. Australasian recommended clinical practice includes medical leadership and family consensus in decision-making. We withdrew intensive therapies in a manner compatible with these principles and practice, because of persistent severe multiple organ failure in 16/145 patients with sepsis and because of severe brain damage (short of brain death) in 66/627 patients with severe TBI, 54/141 patients following resuscitation from cardiac arrest and 32/244 patients following subarachnoid haemorrhage. Ninety-nine percent (166/168) of patients who had intensive therapies withdrawn died shortly thereafter. Two remain disabled – one moderately, the other severely – more than two years later. Of 138 contacted next-of-kin of those who died 123 (89%) "considered themselves well informed" and 120 (87%) "understood the fatal course of events" six weeks after the death.

Conclusion

When severe persistent multiple organ failure or severe brain damage has occurred, withdrawal of intensive therapies is clinically, ethically and legally justified. When it occurs in a structured intensivist-led consensual process, it does not delay death, is accepted by next-of-kin, minimises devastated survivors and husbands scarce and valuable intensive care resources.

End-of-life: a perspective from India

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Ancient religious texts consider death as "Mahaprasthana" or the great departure and even considered voluntary starvation a befitting conclusion to life. However in modern times, the Indian Penal Code states that attempting or abetting suicide is illegal.

When one compares willingness to limit therapy in terminal ICU patients, there is a greater reluctance to do so in India (22% of deaths) compared to more developed countries (74% of deaths). It has been stated that from a relative's perspective, "Indian

sensibilities rarely allow withdrawal of support, and withholding may be more acceptable". Possibly decisions have to do with both "Indian sensibilities" and inadequate communication. In a majority of situations, once communication is clear and family has had time to digest the complexities of the situation, there is a consensus regarding limiting therapy.

Compared to intensivists, referring physicians are generally reluctant to address the issue of DNR. In the general public, the concept of the Living Will is currently non-existent. When bad news needs to be broken, the communication is usually with the relatives and not with the actual patient. It is rare for patients to be told bad news in a free and frank way.

Financial issues have a major impact. In the public hospital system, with little or no direct payments, most decisions are made by the medical community. In the private system, when there is 3rd party payment, relatives are less willing to terminate futile care, while those who are directly paying the bills are more willing to do so. Data from the SAPS III study in Mumbai, India showed that 40-50% of deaths had therapy limited. This occurred in intensivist based ICUs. Outside these setups, it is likely that few are willing to make a decision to institute terminal liberal sedation and extubation. Patients then go through the trauma of being intubated, restrained and receiving little or no sedation at the terminal phase of life. This distressing reality is probably common but inadequately debated or documented.

The Legal Aspects: Article 21 provides right to life, but issues like autonomy and death with dignity have not been adequately explored. Euthanasia and physician assisted suicide are not legal. There is no clarity regarding the legal status of aspects of palliative care like the "double effect" or terminal sedation. Two Supreme Court rulings have given opposing judgments. An earlier one stated that "attempts to hasten death may be viewed as a part of a natural process. A person cannot be forced to enjoy the right to life to his detriment, disadvantage or dislike" while a later one unfortunately took a more rigid interpretation of the law and stated "permitting termination of life in the dying or vegetative, is not compatible with Article 21".

Below are produced two reports. The first is the summary of a recently conducted and published study of EOL care in Mumbai. The second regards a summary of guidelines for terminal care in ICU. These are part of a position statement issued by the Indian Society of Critical Care Medicine (ISCCM).

Kapadia et al. Limitation and withdrawal of intensive therapy at end of life: practices in ICUs in Mumbai, India. *Crit Care Med* 2005;33:1272-1275

Objective: To describe the practices in Intensive Care Units (ICUs) in Mumbai hospitals regarding limitation and withdrawal of care at the end of life.

Design and Settings: Review of prospectively collected data. ICUs of 4 major hospitals (two private tertiary referral general hospitals, one mixed public and private cancer referral hospital and one large public hospital)

Results: The proportion of hospital deaths which occurred in an ICU was 14% in the cancer hospital, 23% in the public hospital vs. 58 & 73 % in the two private hospitals. (Chi-squared test for trends $p<0.0001$)

Of the 143 deaths which occurred in ICU, limitation of care occurred in 49 patients. 25% of these patients were not intubated terminally, 67%, were initially intubated and ventilated but failed to recover and subsequently had no further escalation of therapy, and 8% had withdrawal of therapy. Therapy was limited in 19% of deaths in the public hospital ICU (OR 0.44, 95%CI 0.2 to 0.97) vs 40, 41 and 50% of deaths in the other three ICUs.

*Conclusion*s: Limitation of therapy is done in a significant proportion of ICU patients. Significant differences in the practice of limitation of therapy exist between public and private hospitals. Lack of access to a limited number of ICU beds, especially in the public hospital, may constitute implicit limitation of care.

ISCCM position statement: guidelines for limiting life-prolonging interventions and providing palliative care towards the end of life in Indian Intensive Care Units

1. The physician has a moral obligation to inform the capable patient/family, with honesty and clarity, the poor prognostic status of the patient when further aggressive support appears non-beneficial. The physician is expected to initiate discussions on the treatment options available including the option of no specific treatment.

2. When the fully informed capable patient/family desires to consider comfort care, the physician should explicitly communicate the available modalities of limiting life-prolonging interventions.

3. The physician must discuss the implications of forgoing aggressive interventions through formal counselling sessions with the capable patient/family, and work towards a shared decision-making process. Thus, he accepts patient's autonomy in making an informed choice of therapy, while he fulfils his obligation of providing beneficent care.

4. Pending consensus decisions or in the event of conflicts between the physician's approach and the family's wishes, all existing supportive interventions should continue. The physician however, is not morally obliged to institute new therapies against his better clinical judgment.

5. The proceedings of the counselling sessions, the decision-making process, and the final decision should be clearly documented in the case records, to ensure transparency and to avoid future misunderstandings.

6. The overall responsibility for the decision rests with the attending physician /intensivist of the patient, who must ensure that all members of the caregiver team including the medical and nursing staff represent the same approach to the care of the patient.

7. If the capable patient/family consistently desires that life support be withdrawn, in situations in which the physician considers aggressive treatment non-beneficial, the treating team is ethically bound to consider withdrawal within the limits of existing laws.

8. In the event of withdrawal or withholding of support, it is the physician's obligation to provide compassionate and effective palliative care to the patient as well as attend to the emotional needs of the family.

Experience in the initiation of CRRT in the ICU

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The timing of CRRT is crucial in the treatment of the patient with acute renal failure as it confers a better outcome leading to a higher survival rate. The Surgical Intensive Care Unit (SICU) nurses in the Singapore General Hospital underwent training and certification to allow them to initiate CRRT for the SICU patients who require renal support without the need to wait for the renal nurse from the renal department as was the standard practice before.

The discovery and introduction of ACDA, an anticoagulant that acts by binding free calcium in the blood, to CRRT prevents any clotting from occurring in the hemofilter and circuit allowing continuity of CRRT support that further enhances the survival rate for the acutely renal impaired patient.

Lung protective strategies

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The side effects of positive pressure ventilation are well known. During the 1990s the optimal ventilation strategy in patients with acute lung injury was currently then a subject of much debate. The American College of Chest Physicians Consensus Conference suggested that some of the primary clinical objectives of mechanical ventilation are to: a) reverse hypoxaemia; b) reverse respiratory acidosis; c) relieve respiratory distress; d) preventor reverse atelectasis; and e) reverse respiratory muscle fatigue.

For many years the conventional strategy was to achieve these goals and normalize blood gases using a volume orientated approach to ventilation. It was thought the effects of ARDS on the lung were homogenous, and that ARDS resulted in uniformly "stiff" lungs so that the tidal volume (Vt) was distributed uniformly throughout the lung, and the high peak airway pressure that resulted was considered secondary to the uniformly reduced compliance.

The use of a relatively large Vt (10-15 ml/kg) evolved from anesthesiology practice in patients with normal lungs, after it was shown that a physiological Vt of 5-6 ml/Kg resulted in progressive hypoxemia in such patients.

Today we know from Gattinoni *et al* that the reduced compliance in ARDS occurs because much of the lung is collapsed and not accessible to ventilation, and the Vt is delivered to the small amount of aerated lung. The specific compliance of the aerated lung (compliance per gram of aerated lung tissue) may be relatively normal. So if a volume oriented strategy is used, then it is necessary to set lower tidal volumes in order to prevent alveolar over-distention in the aerated lung.

A large body of evidence now suggests that such overdistension may result in progressive lung injury.

Ventilator-induced lung injury

Extensive evidence from animal studies has clearly shown that mechanical ventilation (MV) can result in acute parenchymal lung injury that is histologically similar to ARDS, in addition to conventional barotrauma.

The lung injury can be progressive and can cause death from respiratory failure. It is also associated with an inflammatory response, and greatly increased concentrations of cytokines have been demonstrated both in lung lavage fluid and in blood in animals ventilated with injurious strategies. MV has also been shown to potentiate the development of bacteraemia after instillation of bacteria into the trachea in animal models.

These findings have led to concerns that MV may augment lung injury, and possibly induce a systemic inflammatory response, which could contribute to the development of the multiple organ dysfunction syndrome (MODS) in patients with ARDS. Thus it has recently been suggested that MV could be a promotor of MODS.

The detailed mechanisms of lung injury and the associated inflammatory response are not yet known.

Two characteristics of the MV pattern appear to be important in determining ventilator-induced lung injury (VILI) in animal models. Firstly, end-inspiratory overdistension causes injury, and greater degrees of overdistension result in more rapid injury. It is clearly a high end-inspiratory lung volume that is important rather than a high end-inspiratory pressure, so the lung injury resulting from this mechanism has been called "volutrauma" to emphasize this mechanism. Secondly, in surfactant-depleted animals, ventilation with low PEEP (and so a low end expiratory volume) also results in injury even without end-inspiratory overdistension. This may be due to repeated end-expiratory collapse and tidal reinflation in some lung regions. It is thought that

this results in very high shear forces at the interfaces between collapsed and aerated lung during reinflation. Sufficient PEEP to prevent end-expiratory collapse largely prevents VILI in animal models when end-inspiratory overdistension is avoided.

Optimum ventilation strategy

These studies suggest that, to avoid VILI, MV should be conducted with sufficient PEEP to prevent end-expiratory collapse and tidal recruitment, and a small Vt to avoid end-inspiratory overdistension.

The dependent lung regions in ARDS are subjected to a superimposed pressure from the weight of the overlying lung, and this tends to result in collapse of these regions at end expiration. Sufficient PEEP to avoid end-expiratory collapse of alveoli or small airways in these dependent lung regions probably results in alveoli in non-dependent regions having a higher than normal end-expiratory volume, because they have less superimposed pressure (and therefore a higher transpulmonary pressure, because static end-expiratory airway and alveolar pressures are equal in all regions). Thus, the nondependent regions are at risk of end-inspiratory overdistension if a normal Vt is used.

In addition, the amount of aerated lung in ARDS is often quite small even with optimum PEEP.

For both reasons, it is necessary to use a low Vt with optimum PEEP to avoid end-inspiratory overdistension, and a Vt of 6 ml/Kg or less is often required.

Gattinoni *et al* suggested that the specific compliance of aerated lung in ARDS is relatively normal. This would mean that overdistension of the aerated lung would occur at a similar distending (transpulmonary) pressure to that producing overdistension in normal lung tissue. This led to the recommendation that the end-inspiratory plateau pressure (PPL) should be limited to 35 cm H_2O, a level thought to be safe in normal lungs.

However, it has been recognized increasingly that the chest wall compliance is low in many ARDS patients, because of chest wall edema and abdominal distension. In such patients a greater than normal proportion of any airway pressure is dissipated in distending the chest wall rather that the lung, and the transpulmonary pressure is lower (and the pleural pressure higher) for any level of PPL. In patients with reduced chest wall compliance, therefore, a higher PPL can be accepted without risk of lung overdistension. Chest wall compliance and transpulmonary pressure can be estimated using an esophageal balloon, or alternatively a reduced chest wall compliance can be assumed in patients with abdominal distension and chest wall edema.

The PPL is usually measured to estimate lung distension rather than the peak inspiratory pressure (PIP), because the latter is affected by changes in airway and endotracheal tube resistance; thus a high PIP may not necessarily reflect excessive lung distension. The PPL is not affected by resistance, as it is measured during no flow conditions.

Selection of PEEP

Many approaches to selecting PEEP have been suggested. In the past, the emphasis was on optimizing oxygenation (either SaO_2 or oxygen delivery). More recently, the concept of using a "lung protective strategy" by preventing end-expiratory collapse has been proposed. The best method of determining the level of PEEP required to achieve this remains unclear. It has been suggested that the lower inflection point (Pflex) of the static pressure-volume (PV) curve represents the pressure range over which recruitment of previously collapsed lung occurs, and so setting PEEP above the lower Pflex should prevent end-expiratory collapse.

It has also been suggested that the upper Pflex represents the pressure range above which lung overdistension occurs, and that the PPL should be limited to this pressure. However, these concepts may be over simplistic. A mathematical model of ARDS lungs developed by Dr Keith Hickling suggests that the lower Pflex may represent only the beginning of recruitment, and recruitment may continue on the linear portion. It also suggests that the slope of the linear portion of the PV plot may be greater than the compliance of all aerated alveoli, because of recruitment, and that an upper Pflex may occur at low pressures as recruitment diminishes, even in the absence of lung overdistension. An upper Pflex that is related to overdistension may be greatly modified or even obliterated by continuing recruitment.

The model suggests that the PEEP level giving "best compliance" may also be misleading, and may overestimate or underestimate optimum PEEP. Thus, the PV curve measured at zero PEEP may not predict optimum ventilator settings; further studies are needed to clarify these issues. PV curves at incremental PEEP levels may be more helpful, but measurement of absolute lung volume is probably the most reliable approach to detecting the optimum PEEP to prevent end-expiratory collapse.

With this approach, "optimum PEEP" is indicated by the PEEP level giving the maximum absolute lung volume at a pressure of 15 or 20 cmH_2O (or the pressure of the highest PEEP level evaluated) during inspiration this approach is satisfactory.