The capillary leak of ALI/ARDS

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Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) refer to a clinical syndrome, defined by signs and symptoms that are thought to indicate increased permeability (as opposed to cardiogenic or hydrostatic) pulmonary edema and can be caused by a variety of conditions including pneumonia, sepsis, near-drowning, trauma and others. Although only 75% of patients meeting clinical (consensus) criteria for ALI/ARDS have a measurable increase in (thermal dilution) extravascular lung water, most patients have an increase in protein permeability in the lungs, as assessed with help of a bedside dual radionuclide technique. The equipment necessary for the measurement of the transferrin pulmonary leak index (PLI) is simple and cheap. Indeed, the technique may help to separate permeability from hydrostatic pulmonary edema in difficult cases. The PLI also parallels the clinical severity and course of ALI/ARDS and may thus constitute a useful measure to evaluate new therapies, independently of the crude assessment by clinical criteria only, as expressed in the lung injury score, that may not be independent of ventilatory therapy. The measure may be sensitive to subclinical forms of transient pulmonary (alveolocapillary) injury, for instance after cardiac or major vascular surgery. Finally, the method has helped us to decide on the pathogenicity of herpes simplex virus-type 1 recovered from tracheal aspirates or bronchoalveolar lavage fluids in mechanically ventilated patients with otherwise unexplained persistent pulmonary infiltrates on chest radiography.

The heart in sepsis

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During sepsis, circulatory alterations that lead to hypotension, ie septic shock, include fall in peripheral vascular tone in many vascular beds, and an early (but transient) fall in myocardial function. The latter can be characterized by a low ejection fraction, low preload-recruitable cardiac output and stroke work, ventricular dilatation and changes in compliance, thus encompassing altered systolic and diastolic function of the ventricles. If shock is complicated by pulmonary arterial hypertension, and mild forms are relatively common in septic shock, dilatation of the right ventricle may ensue and jeopardize subendocardial perfusion. Superimposed right ventricular dysfunction can complete the full picture of the myocardial depression of septic shock. The myocardial depression may occur even in the presence of a hyperdynamic circulation with a high cardiac output, but may hamper a further increase with (colloid) fluid loading, the first step in treating the syndrome. The pathogenesis of the reversible myocardial depression of septic shock is complex and involves cytokine-induced myocardial upregulation of inducible NO synthase, increased release of NO, which acts on guanylate cyclase and cGMP and relaxes the muscle by interfering with Ca^{2+} transients and myofilament sensitivity. Altered coronary vascular reactivity may lead to intramyocardial maldistribution of blood flow and focal ischemia. Methylene blue, a guanylate cyclase inhibitor, may partially reverse the myocardial depression, as suggested by some studies on human septic shock. Although the peripheral abnormalities of septic shock are major determininants of the prognosis, the cardiac alterations may complicate treatment and occasionally result in refractary circulatory collapse.

IHD, CRRT and SLEDD

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Acute renal failure (ARF) is frequent in the intensive care unit (ICU). Renal replacement is usually delivered in one of two ways: intermittently with haemodialysis (IHD) or continuously (CRRT) with veno-venous haemofiltration (CVVH) or haemodiafiltration (CVVHD). IHD depends on diffusion with solute transport across a semi permeable membrane generated by the concentration gradient at a rate inversely proportional to the molecular weight. CVVH, on the other hand, relies on convection where solute and water move across a much more permeable membrane which allows the passage - solute drag - of molecules of up to 20,000 daltons.

Which technique is chosen depend on the particular set of circumstances of each intensive care unit. In Australia many ICUs have developed without access to IHD and continuous techniques are almost universal whereas IHD predominates in the US and both are common in Europe. The advantages and disadvantages of each are widely debated.

CRRT is suitable for haemodynamically unstable patients. Continuous therapy avoids periods of hypotension and dehydration, which may worsen ARF. It offers precise fluid, urea and electrolyte control. It may have non-renal advantages. Less nurse training is required. Its disadvantages include the need for anticoagulation, hypothermia, electrolyte depletion and cost both in terms of capital cost of equipment and fluids. The disadvantages of IHD include haemodynamic instability, dehydration, episodic and less effective solute removal and acid base control as well as limited role in controlling middle molecules. IHD does not require expensive replacement fluids.

While the debate continues there is little evidence for the superiority of either technique. There has recently been the development of 'hybrid techniques' - such as slow low efficiency daily dialysis (SLEDD) - which aim at combining the best features of both IHD and CRRT. SLEDD uses a standard dialysis machine, online dialysate production but slower blood and dialysate flows than IHD. The duration of dialysis is about 8-12 hours, usually overnight. Overnight dialysis is a major advantage in that this frees the patient for investigations and procedures during the day. Advantages put forward for SLEDD include economy, less haemodynamic instability and excellent solute control: it is likely to be used more in the future.

Controversial issues in treatment of hyperkalemia

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Hyperkalemia is a frequently encountered medical emergency that can lead to life-threatening cardiac arrhythmias. The acute management of emergency hyperkalemia remains controversial and is the focus of this review. We will begin by discussing the principles of extra renal potassium homeostasis, continue by examining the evidence for therapies proposed to enhance extra renal potassium disposal (intravenous insulin and glucose, β_2-agonist, and $NaHCO_3$) and conclude with a discussion of the role of cation exchange resins in the treatment of hyperkalemia. To allow more K^+ to enter cells, there must be an increase in the cell interior negative voltage. This would occur if Na^+ ions were exported from the cell by the Na^+/K^+-ATPase at a faster rate. The Na^+/K^+-ATPase can be activated either by increasing the availability of intracellular Na^+ or directly via phosphorylation (β_2-agonists). For the net export of positive charges out of the cell, however, the extruded Na^+ must be the ones that were either already inside the cell or entered the cell electroneutrally, for example via the Na^+/H^+ exchanger(NHE-1). The major activators of NHE-1 are intracellular acidosis and insulin. Overall, the studies reviewed support the use of regular insulin (20 U i.v. bolus) with glucose as the first-line management of acute hyperkalemia. Insulin lowers the plasma $[K^+]$ by 0.5-1 mmol/l with 15-30 minutes. Nebulized β_2-agonists lower plasma $[K^+]$ to a similar degree as insulin, but are ineffective in 20%-40% of patients with uremia and question still remain about their safety. The use of $NaHCO_3$ remains debatable as the data for and against its use were obtained under circumstances that do not resemble the usual clinical setting of acute emergency hyperkalemia. We use $NaHCO_3$ in the treatment of emergency hyperkalemia in patients with a significant degree of acidosis; however, not as the only therapy. Lastly, cation exchange resins are not effective in the treatment of acute hyperkalemia. For the management of chronic hyperkalemia, the addition of resins to cathartics does not significantly enhance fecal K^+ excretion beyond the effect of diarrhea induced by osmotic or secretary cathartics alone.

Lactate: A preferable energy substrate in the brain

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For many decades, lactate was considered to be an end product of anaerobic glycolysis with no other function in metabolism. As the measurement of lactate in hospital blood work became routine, fluctuations in its levels were associated with situations other than oxygen deprivation. Thus, it was just a matter of time before elevated lactate blood levels emerged as a 'red flag' for potential malaise and frequently was blamed as the 'cause' of it. The 'anti-lactate' attitude, especially among clinicians, has been difficult to change, despite recent findings that strongly indicate lactate to be a possible beneficial intermediate in brain energy metabolism. As early as 1953, *in vitro* studies demonstrated that neuronal tissue is capable of respiring with lactate as a substrate. Thirty five years later it was also shown *in vitro* that lactate can support neuronal function as the sole energy substrate. This finding led to a series of *in vitro* and *in vivo* experiments leading to the conclusion that lactate is both a preferable energy substrate over glucose in neuronal tissue and that it is most likely an obligatory energy substrate for recovery of brain function from ischemia/hypoxia. To fully comprehend the transformation in our understanding of lactate's role in brain energy metabolism and its meaning for the medical community, a review of these studies is necessary, especially in light of a study that was published in 2003 which demonstrated lactate to be a preferred fuel for human brain metabolism *in vivo.*

Management of Disseminated Intravascular Coagulation in the ICU

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Not uncommon in the ICU, Disseminated Intravascular Coagulation (DIC) complicates a variety of clinical conditions such as sepsis, trauma and obstetric emergencies. In prospective trials in sepsis and trauma, the development of DIC doubles the risk of death. By far the most common trigger for DIC is tissue factor (TF) exposure to the blood. TF is a membrane bound glycoprotein normally not in direct contact with blood, that when exposed to blood, rapidly binds to FVIIa and triggers the extrinsic coagulation cascade resulting in thrombin formation. In sepsis, one of the more common causes of DIC, the release of TNF and IL-6 will lead to up-regulation of TF and PAI-1 and down-regulation of thrombomoduline. This sets the scene for a pro-coagulant state where the PC/PS control system is down regulated and fibrinolysis is suppressed by PAI-1.

The balance between thrombin and plasmin determines the clinical presentation: thrombosis or bleeding. The laboratory presentation varies between chronic low-grade and acute DIC. In low grade chronic DIC present in certain types of malignancy, retained dead fetus and other conditions, only FDP may be elevated. By contrast, in acute severe DIC of sepsis, delayed shock resuscitation, trauma and obstetric complications platelets and fibrinogen are consumed faster than they are produced. This leads to thrombocytopenia and low fibrinogen levels with high FDP, D-dimmers as well as soluble fibrin monomer and thrombin-antithrombin complex levels.

Data from a patient who developed DIC will be presented. The ICU management of these acute DIC patients should initially include restoration of blood volume, identification and addressing the triggers for DIC as well as restoring the hemostatic potential by transfusing blood platelets and fibrinogen (cryoprecipitate) when necessary. In selected patients, heparin therapy may be helpful, indications and contraindication will be reviewed. Antifibrinolytics are usually contraindicated.

Recent trial results for AT, APC, TFPI will be discussed. In particular, APC may be helpful in controlling DIC that does not respond to conservative treatment.

Advance directives in the Intensive Care Unit

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As medical technology advances, patient with chronic or terminal disease and their physicians are confronting decisions regarding high technology therapies and procedures that may offer small or no benefit to their quantity or quality of life. When physicians take into consideration the good of society and the good of their patients, they may have to make extremely difficult decisions with regard to continuation of life support in the face of poor prognosis and limited space in the intensive care unit.

Advance care planning (ACP) is becoming increasingly important because of the aging population, the increasing ability of medical care to keep patients alive and the emphasis on patient autonomy as a dominant principle in medical decision-making. Advance directives (AD), including living wills and durable healthcare power of attorney, arising as a result of advance care planning, are based on the recognition and acceptance of patient autonomy and on the assumption that patients can anticipate their choice under circumstances where death is imminent.

The 1990 USA Patient Self–Determination Act, seeks to increase patient involvement in decision regarding life sustaining treatment by insuring that advance directives for health care available to physicians at the time medical decisions are being made.

The medical profession must realize that, despite tremendous advances in medical knowledge and technology, not everyone can be saved all the time, even in the area of ICU. Physician must understand that "doing everything that is best for the patient may rather imply moving from a process of curing to caring with palliative care. This process should be initiated by the discussion with the patients or surrogate and should include knowledge of the patients' wishes as demonstrated by advance directive and durable power of the attorney.

After we applied the documented informed consent for admission to the ICU, Severance Hospital Yonsei University College of Medicine from March 1st, 2003, the incidence of advance directives by patients and family as do not attempt resuscitation (DNAR) and no renal support therapy were more frequent. Duration of ICU stay was shorter and more patients admitted with lower mortality rate also after then.

Hypertonic lactate versus mannitol in head trauma

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Mannitol remains widely used to decrease intracranial pressure (ICP) in patients with head injury. The mechanism by which this solution exerts its effects is not totally understood. Among them, the most famous is the osmotic effect leading to a delayed and prolonged decrease in both cerebral water content and ICP, providing blood brain barrier is intact. Some studies have reported that the initial rapid decrease in ICP has three additional mechanisms: a decreased cerebrospinal fluid volume; a cerebral vasoconstriction due to an increased cerebral blood flow secondary to a decreased blood viscosity, and an improved systemic hemodynamic. However, some patients presented with a refractory intracranial hypertension. Moreover, mannitol can lead to plasma hypertonicity and its beneficial; effects are transitory with a rebound increased ICP. Recommended doses are between 0.25 and 1 g/kg with a 4 hours delay between 2 infusions and a maximum cumulative dose of 200 g per day.

Contrary to an old concept, lactate has been demonstrated to be non toxic for brain. Moreover, in a model of cerebral ischemia-reperfusion, it has been reported that lactate represents a major obligatory oxidizable substrate. In this model, lactate which is preferentially used during reperfusion, improved neuronal function recovery. Considering these data, we hypothetized that hypertonic lactate infusion might decrease ICP while improving cerebral energy metabolism. Thus, we performed a prospective randomized study in severe head trauma, comparing cerebral hemodynamic and energy metabolism effects of mannitol and hypertonic lactate. We found that the decreased ICP was significantly higher and longer with hypertonic lactate than with mannitol. There was more failure in treating intracranial hypertension with mannitol than with hypertonic lactate. Lactate was metabolized and the decreased lactate on pyruvate ratio indicated that brain was able to oxidize lactate despite intracranial hypertension.

In summary, hypertonic lactate seems to have beneficial cerebral hemodynamic and metabolic effects. Further studies must be performed to confirm these data.

Ketoacidosis

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We shall illustrate that management of patients with metabolic acidosis could be improved with the use of a quantitative analysis based on understanding of basic concepts of metabolic regulation. A case of an elderly cachectic woman is presented to illustrate some of the important biochemical and metabolic aspects of alcoholic ketoacidosis. A point to emphasize is that an interplay of signals related to hormonal regulation and controls exerted by the rate of turnover of ATP in hepatocytes sets the stage for ketogenesis and also limits its maximum possible rate. The severity of ketoacidosis is a function not only of the rate of production of ketoacids but also the ability to dispose of H^+ via buffering and metabolism of ketoacid anions. Buffering of H^+ is beneficial if H^+ is buffered by the bicarbonate buffer system rather than by intracellular proteins. This latter function depends on having a low tissue PCO_2 due to a combination of hyperventilation plus an adequate blood flow rate to vital organs. H^+ is removed when the accompanying anion is metabolized to a neutral end product or is excreted in the urine with H^+ or ammonium ($NH4^+$). The rate of removal of H^+ via the metabolism of ketoacid anions is determined by the rate of turnover of ATP in consuming organs, mainly the brain and the kidney. A decrease in energy demand in one or both organs can lead to a diminished rate of oxidation of ketoacids and hence a more severe degree of acidosis. Further, while ketogenesis occurs without a lag period when ethanol is the substrate, this is not matched by a rapid rate of removal, as there appear to be a lag period before the brain is fully adapted to the use of ketoacids. A component of the metabolic acidosis in patients with ketoacidosis is due to an ”indirect loss of $NaHCO_3$“, the correction of this HCO^{3-} deficit requires new HCO^{3-} generation by the kidney with the excretion of NH_4Cl in the urine.