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Year in review in intensive care medicine, 2004. II. Brain injury, hemodynamic monitoring and treatment, pulmonary embolism, gastrointestinal tract, and renal failure

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This review intends to summarize all articles published in *Intensive Care Medicine* in 2004, grouped by specific topics

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Brain injury

The mismatching of demand and supply for organ donation has been highlighted in *Intensive Care Medicine* this year. A group from Paris [1] reported on their survey of patients admitted in severe coma in which they examined the implications for brain death identification and organ donation. This well conducted survey concludes that increasing the number of hospital donor/transplant coordinators in collaboration with mobile emergency units had led to identification of more comatose patients in ICU and more brain-dead patients. This endeavor had a direct effect on increasing the organ donation rate. This interesting report was accompanied by an editorial by Park [2]. The mismatch between demand and supply of organs was commented upon again and alternatives considered. These of course include living relative donation and the attendant risk of surgery, anesthesia, and postoperative care of the previously well donor. Opting-in, opting-out, presumed consent, and the logistics of donating nonbeating hearts were reviewed. While both of these contributions are commendable, one may be led to the conclusion that the diagnosis of brain death (or brainstem death) is made to facilitate organ donation. In an editorial entitled "Brain death" Russell [3] emphasizes the importance of making the concept of brain death a reflection of our moral and philosophical ideas of what it means to be alive or dead and should not in any way be linked to the need for organ donation/transplantation and that a human being should be declared brain dead only because he/she is in fact dead. The concept of brain death that is in use should not be influenced by any other criteria, regardless of important such criteria may be to other human beings.

Processed electroencephalographic (EEG) monitoring in the intensive care setting presents a considerable challenge to already overburdened care givers at the bedside. In an interesting trial Leira et al. [4] noted that recognition of epileptiform changes by bedside caregivers is very low and showed that a simple educational intervention only modestly improves this ability. They concluded that no reliance should be placed on nontrained personnel to interpret emergent or continuous EEG recordings. The issue of the training and expertise required to interpret nonprocessed EEG recordings is important, and therefore it is reassuring that highly processed EEG recordings may have a role in critical care, assessing responsiveness or depth of sedation in intensive care unit patients. Schneider et al. [5] evaluated the Patient State Index by comparing it with the Ramsay score assessed by the bedside caregiver, and the data were analyzed using a general linear model. Increasing depth of anesthesia monitors were assessed using pharmacokinetic assessment. This analysis demonstrated a high prediction probability, and the authors concluded that the Patient State Index may be used to quantify the level of propofol/sufentanil sedation in intensive care unit patients. This issue was addressed in a commentary by Walsh et al. [6] that questioned the role of "black boxes" in intensive care units. The clinical utility of these black boxes clearly needs regular assessment, and the processing should not be assumed as it requires rigorous scrutiny. To emphasize this point, Ely et al. [7] assessed the utility of the BIS-XP software revision of the bispectral index for quantifying "consciousness" in ventilated patients. The BIS-XP algorithm demonstrated a stronger correlation with RASS levels (agitation and sedation score) than previous software revisions but still marked overlap occurred between different levels of arousal. The authors conclude that after controlling for the level of arousal neither the BIS-XP nor the BIS 3.4 algorithm distinguishes between the presence and the absence of delirium. Sedation practice is fundamental to intensive care, and data on dexmedetomidine support further investigation [8].

Traumatic brain injury was the focus for a number of contributions in the previous year of *Intensive Care Medicine*. Assessments have been made of physiological derangement, including prediction of "early" hyperthermia [9] and endocrine disturbances [10], showing that the most common abnormalities include cortisol hyporesponsiveness and hypogonadism. These neuroendocrine responses are important as it is believed that the hippocampus is susceptible to high levels of free cortisol [11, 12] and may be increasingly vulnerable when associated with low arterial pressure and oxygenation and low androgenic steroid levels.

Intensive care management of cerebral oxygen delivery and variability in response to vasopressor or inotrope infusion [13, 14] and hyperventilation [15] was evaluated. The authors concluded that regional response to dopamine and/or norepinephrine support of the cerebral perfusion pressure can lead to unpredictable effects as can hyperventilation, and thus change in therapy requires close invasive monitoring. The European Brain IT Centres published the outcome of a survey on traumatic brain injury (TBI) from 2001 [16]. This multicenter, multicountry data collection exercise was supported by the European Framework. Despite recruitment of academic centers there was considerable variation in clinical practice; however, the authors concluded that management of TBI is mainly in accordance with published guidelines but with some deviation. Particularly the suggested order and combinations of different treatments varied. This data collection exercise continues under the leadership of the Steering Committee and forms an infrastructure for future randomized controlled trials.

The effects of expiratory tracheal gas insufflation in patients with severe TBI and acute lung injury were examined by Martinez-Perez et al. [17]. They examined the effect of phasic tracheal gas insufflation at middle to end expiration in patients with severe head injury and acute lung injury/acute respiratory distress syndrome. Patients

were all ventilated in the assist/control mode to achieve adequate oxygenation and normocapnia. Expiratory tracheal gas insufflation at 8 l/min flow rate was delivered for 90 min with normocapnia maintained by simultaneous reductions in tidal volume. They concluded that in this TBI patient group with acute lung injury expiratory gas insufflation allowed the maintenance of target $PaCO_2$ levels with a substantial reduction in tidal volume and protection of the lung. It will be interesting to see whether this becomes incorporated into clinical practice; however, before this is likely to happen a large prospective trial is needed.

Subarachnoid hemorrhage is a major challenge to the critical care departments of hospitals admitting such patients. The high mortality from the initial bleeding, rebleeding, and subsequent vasospasm and complications of the disease (including hydrocephalus and cardiogenic shock) require motivated and dedicated multidisciplinary teams. The incidence of the phenomenon of hyperemia following subarachnoid hemorrhage has been well described but is frequently over looked. Rothoerl et al. [18] assessed hyperemia using transcranial Doppler ultrasound and xenon 133 clearance to measure cerebral blood flow. They concluded that global hyperemia is a common phenomenon and is correlated positively with favorable outcome and cannot be detected by standard transcranial Doppler ultrasound measures or clinical examination.

In the 2004 year review, neurology and neurological monitoring in intensive care provide further small pieces in the jigsaw of understanding the pathophysiology and the relationship with functional recovery after brain injury. Observational databases and small prospective pragmatic trials make up the majority of submissions, with few randomized controlled trials. A neglected group are the subarachnoid hemorrhage patients, who currently are managed largely by neuroradiologists inserting GD-detachable coils to secure the aneurysmal sac. The results of the ISAT trial have turned the focus of treatment to patients with good grade (World Federation of Neurological Surgeons scale) with aneurysms of the anterior circulation and favorable neck morphology. With high-quality data on functional recovery from ISAT, interventional radiologists now aspire to achieving similar results. We believe that these pressures have resulted in a neglect of poor grade patients, despite a potential 50% good functional recovery, if actively managed [19]. Sadly, our personal observation is that these patients are now suffering more neurological deficit and death from rebleeding because they have a low priority for the definitive caregivers, neuroradiology and neurosurgery. A systems approach is necessary to improve the care of these vulnerable patients. We believe that neurological intensive care has an important role in advocacy, making the case to patients/relatives, the public, policy makers, and other healthcare professionals that complex, life-threatening neurological diseases are best cared for by a multidisciplinary team including specialized expertise in neurological critical care.

Hemodynamic monitoring and treatment

Last year saw the publication of several important studies addressing fundamental aspects of hemodynamic monitoring. Hemodynamic monitoring is a central aspect of cardiovascular diagnosis and titration of care. In the arena of invasive monitoring alternatives to pulmonary arterial catheterization have been sought for a variety of reasons. Combes et al. [20] demonstrated in 333 mechanically ventilated patients that a single transpulmonary thermal injection from a central venous site using the PiCCO system provides estimates of cardiac function index and global ejection fraction that are similar to measures of left ventricular (LV) ejection fraction made by transesophageal echocardiography (r=0.87 and 0.82, respectively). These data are exciting because they suggest that estimates of LV systolic function can be made without the need of a pulmonary artery catheter. There are two caveats that need to be underscored. First, these workers carefully excluded patients with right ventricular (RV) dysfunction because PiCCO-derived parameters include RV function whereas echo-derived measures are specific for LV performance. Accordingly, care must be used when applying this measurement technique across a wider group of mechanically ventilated patients, many of whom may have RV dysfunction associated with acute respiratory failure. Furthermore, measures were made only once per subject, not as systolic function was systematically varied, for example, by fluid resuscitation and infusion of inotropic agents. Thus it is not clear what degree of sensitivity these global measures will enjoy when tracking changes in systolic function over time.

Similarly, increased interest in the use of central venous O_2 saturation ($ScvO_2$) as an estimate of mixed venous O_2 saturation (SvO_2) has emerged following the introduction of the central venous fiberoptic O_2 saturation catheter. In the nonexercising subject decreases in SvO_2 up to 70% connote tissue hypoxia. Reinhart et al. [21] compared the two O_2 saturation measures in 29 patients with both catheters followed continuously for over 1000 h, making both fiberoptic and in vitro measures of venous O_2 saturation. These workers found that the central venous O_2 catheter more accurately estimates $ScvO_2$ than spot in vitro measures and is not affected by simultaneous infusion of fluids through the catheter or by changes in hematocrit, hemoglobin, temperature, or blood pH. More importantly, $ScvO_2$ tracked SvO_2 but tended to be 7±4% higher. Furthermore, changes in $ScvO_2$ paralleled SvO_2 changes 90% of the time when SvO_2 changed by 5% or more. These data suggest that if one needs to identify an SvO_2 change of at least 5%, $ScvO_2$ monitoring is accurate most of the time. However, if threshold values

of $ScvO_2$ are to be used to guide therapy, care must be taken to ensure sufficient sensitivity in an individual patient to detect potential tissue hypoperfusion.

Extending backward from pulmonary artery catheter to central venous catheters, Desjardins et al. [22] examined the ability of anticubital vein transduced pressure to reflect central venous pressure (CVP) from a total of 188 measurements in 19 cardiac surgery patients. CVP varied by treatment and the use of mechanical ventilation. These workers found that the two pressures were interchangeable, with a pressure differences between 0.72 and 0 mmHg. These values are well within the level of measurement error of either device alone. Thus if measures of CVP need to be assessed, as may be the case in assessing effective circulating blood volume, peripheral venous pressure is a readily available surrogate for CVP. Unfortunately, these workers did not report the changes in peripheral venous pressure and CVP during spontaneous ventilation. Spontaneous inspiration-associated decreases in CVP can be used to identify preload responsiveness. Theoretically one would not expect peripheral venous pressure to accurately reflect CVP changes because of the compliance of the peripheral venous compartment and the probability of vascular collapse as CVP decreases below zero during inspiration. Thus the usefulness of this estimate of CVP will need to be examined in a subsequent study.

Noninvasive measures of central hemodynamic values have become increasingly available with the advent of newer devices and new applications of established monitoring devices.

In an attempt to bypass invasive catheterization completely Staal et al. [23] compared angiographically measured LV volumes using Simpson's rule, with transcardiac conductance measured from surface skin electrodes in ten subjects undergoing angiography. Reliably stable data were available in eight of the subjects and gave good agreement in terms of LV volumes (R^2=0.78). This technique has the added potential advantage of also providing continuous monitoring of LV volumes, although that aspect of this technology needs to be validated in future studies.

Along similar lines of reasoning, pulse dye density in which one measures peripheral blood dye density noninvasively following a bolus infusion of indocyanine green dye into a central vein, allows the measurement of both central blood volume (initial dilution) and circulating blood volume (steady-state dilution). Bremer et al. [24] measured both these variables in cardiac surgery patients before and following surgery as intravascular volume resuscitation was performed. Surprisingly, they found that, despite fluid resuscitation, circulating blood volume decreased, while central blood volume did not change. The functional significance of these profound changes in blood volume distribution is unclear since there were no outcome measure differences between subjects based on the decrease in circulating blood volume. Since central blood volume is a close approximation of ventricular preload, this significance of changes in circulating blood volume independently of central blood volume is unclear.

Instead of using indocyanine green dye as an indicator one can potentially use less expensive and more readily available markers. Glucose is one such marker. Gabbanelli et al. [25] used a bolus glucose technique to estimate central blood volume and compared it to PiCCO-derived measures of central blood volume daily for 5 days in 20 critically ill patients requiring invasive hemodynamic monitoring. They observed a good correlation between the two techniques (R^2=0.79).

Remaining with noninvasive monitoring, Spadetta et al. [26] applied an old technique, known partial CO_2 rebreathing, to assess cardiac output in 12 ventilated patients. Patients were stratified in advance into those with high [6] and low [6] intrapulmonary shunts. They found that the technique accurately parallels thermodilution cardiac output estimates of cardiac output in subjects with low intrapulmonary shunts. However, when subjects had a high intrapulmonary shunt (>35%), CO_2 rebreathing underestimated true cardiac output. Since many of the intubated and ventilated patients needing cardiac output measures have acute lung injury with increased intrapulmonary shunts, the clinical utility of this simple technique in those patients is questionable. However, in all other subjects this technique reflects a reasonable noninvasive approach to monitoring cardiac output in the critically ill, ventilator-dependent patient.

Echocardiography is a minimally invasive (transesophageal) to noninvasive (transthoracic) technique enjoying increased popularity in recent years, as intensivists start taking it to the bedside of their critically ill patients. Novel uses for this imagining technique are evolving with exciting potential for patient care. In a series of studies from the Jardin group [27] threshold estimates of CVP were made by observing the behavior of the great veins during positive pressure ventilation to predict preload responsiveness. Viellard-Barton et al. [27] measured superior vena caval collapse using transesophageal echocardiography in 66 successive ventilated septic patients before and after an intravascular volume challenge. They found that superior vena caval collapsibility greater than 36% predicted an increase in cardiac output of at least 11%, with a 90% sensitivity and a 100% specificity. Furthermore, Barbier et al. [28] measured inferior vena caval collapse using transthoracic echocardiography in 23 successive ventilated septic patients before and after an intravascular volume challenge. The found that inferior vena caval collapsibility greater than 18% predicted an increase in cardiac output of at least 15%, with a 90% sensitivity and specificity. These two reports prompted an editorial by Vignon [29], who noted that these measures carry with them the same limitations as do any of the previously published arterial pressure variation parame-

ters, namely a dependence of the level of tidal volume and its regularity without spontaneous ventilatory efforts, the separation of preload-responsiveness by need for fluid resuscitation, and the dependence of a normally functioning right ventricle to relate these measures into changes in cardiac output. These points have been raised before in this *Journal* [30].

Echocardiography can also measure tissue movement using Doppler techniques. Although routinely used to identify regurgitant flow and assess pulmonary arterial pressure, when Doppler methods are applied to tissue movement, a stronger signal but at a much slower velocity can be assessed. Combes et al. [31] used both transthoracic and transesophageal echocardiography to measure the ratio of the mitral inflow E wave velocity to early diastolic mitral annulus velocity (E/E′) to estimate pulmonary artery occlusion pressure in 23 consecutive mechanically ventilated patients in whom volume expansion was then given to 14. They observed a good correlation between E/E′ using either the medial or lateral side of the mitral annulus by both transthoracic and transesophageal echo techniques accurate in predicting a pulmonary artery occlusion pressure of 15 mmHg or higher. Although somewhat specialized in its measurement, tissue Doppler imaging is actually easier to perform than blood flow velocity studies. Thus as more intensivists start to become familiar with this technique, use of the E/E′ ratio to define preload may become increasingly popular. Bedside echocardiography is clearly becoming a major diagnostic tool for the intensivists, and the usefulness of this tool is expanding rapidly as we include functional measures of performance to supplement the structural observations commonly reported.

Doppler technology is not limited to echocardiography. Esophageal Doppler monitoring (EDM) probes capable of measuring descending aortic velocity and flow are commercially available. Dark and Singer [32] performed a systematic search of the relevant international literature on this approach, finding 21 studies encompassing 314 patients including 2,400 paired measurements of cardiac output by thermodilution and EDM. Importantly, these workers showed that although EDM does not measure absolute cardiac output, the changes in cardiac output observed by thermodilution are closely paralleled by the changes in EDM. The pooled mean bias for thermodilution to EDM was 0.19 l/min (range −0.69 to 2.00 l/min) whereas the pooled mean percentage of clinical agreement between the two measures was 52% for absolute cardiac output and 86% for changes in cardiac output. Since newer monitoring approaches underscore the importance of noting changing cardiac output over absolute values, these findings demonstrate that the EDM technologies can be used to monitor changes in cardiac output.

In an unrelated area, Bahmann et al. [33] assessed myocardial redox state using myocardial lactate/pyruvate ratios collected by microdialysis in 17 patients under going cardiac bypass surgery. They demonstrated that this ratio progressively increased from 11 to 34 consistent with decreased redox state during bypass. The clinical utility of this in patients undergoing cardiac bypass was not addressed in this study. However, lactate to pyruvate ratios is an excellent marker of tissue redox state and could be used in the future to determine cardiac perfusion in complex patients.

Finally, hyperlactatemia is a common characteristic of patients with sepsis or acute respiratory distress syndrome and in subjects undergoing cardiopulmonary bypass. Previous studies have documented that the lung is the primary source of lactate production in patients with acute respiratory distress syndrome. Bendjelid et al. [34] wondered whether the hyperlactatemia following cardiopulmonary bypass has a similar origin. They measured the step-up in blood lactate levels between mixed venous and arterial blood 16 patients after cardiopulmonary bypass and observed a positive lung lactate flux that was not proportional to total time on bypass or aortic cross-clamp time. The authors concluded that pulmonary release of lactate is a major source of blood lactate in this patient population. These findings are important because intensivists tend to use blood lactate levels as a marker of tissue hypoperfusion. Although tissue hypoperfusion can cause hyperlactatemia, this study shows that hyperlactatemia need not reflect hypoperfusion, but rather occult lung injury.

Pulmonary embolism

The use of thrombolytic agents is widely recommended in patients with shock and hypotension secondary to massive pulmonary embolism (MPE). One of the most important points suggesting the use of thrombolytic agents in MPE is their potential immediate hemodynamic effects on pulmonary and systemic hemodynamics. Podbregar et al. [35] evaluated the role of the characteristics of the central pulmonary thromboemboli to predict hemodynamic response to thrombolysis in MPE. Using transesophageal echocardiography the authors identified two kinds of thrombi, mobile and immobile, in 12 consecutive patients with MPE, before urokinase administration through the central venous port of the pulmonary artery catheter. Despite the small number of patients included in each group (n=6) their results suggest that the presence of mobile thrombi is associated with an earlier hemodynamic stabilization, a reduction of 52% in the total pulmonary vascular resistance index 2 h after the onset of thrombolysis in patients with mobile thrombi, vs. 15% in patients with immobile thrombi (p=0.04). A lower cumulative dose of urokinase and duration of thrombolysis were simultaneously reported in patients with MPE and mobile thrombolysis. These preliminary results thus

reemphasize the value of transesophageal echocardiography not only in diagnosing the presence of acute cor pulmonale but also in determining the precise characteristics of central pulmonary thromboemboli to try to predict the hemodynamic response to thrombolytic therapy.

This study suggested that hemodynamic monitoring with pulmonary artery catheter of patients with MPE is of paramount importance; however, the use of this invasive device in patients receiving thrombolysis is a matter of controversy. Increased alveolar dead space from unperfused but well ventilated lung regions is a major characteristic of MPE. Verschuren et al. [36] reported two cases of spontaneously breathing patients suffering from MPE in which successive capnographic measurements were performed before, during, and after thrombolysis. To do this, Verschuren et al. [36] used the technique of volumetric capnography, the plot of expired CO_2 concentration against expired volume. They observed a decrease in the late deadspace fraction in their two patients, correlated with a concomitant disappearance of RV dysfunction on transoesphageal echocardiography. These authors considered that the technique of volumetric capnography is more appropriated than CO_2–end-tidal CO_2 gradients in spontaneous breathing patients and/or in patients with chronic obstructive pulmonary disease. If validated in a large cohort of patients, this noninvasive technique may prove helpful for the assessment of the therapeutic efficacy of thrombolysis.

Brain natriuretic peptide

Brain natriuretic peptide (BNP) and its precursor N-terminal pro-BNP have been considered as effective markers for the diagnosis of the cause, i.e., cardiac of respiratory, of an acute respiratory failure and for the severity and prognosis of acute coronary syndromes and heart failure. Kerbaul et al. [37] performed a 12-month prospective study in 60 adult patients undergoing coronary artery bypass grafting by the off-pump technique to determine the respective roles of N-terminal pro-BNP, procalcitonin, and troponin I to predict the onset of postoperative cardiac events. Using receiver operating characteristic curves (receiver operating characteristic curves) their study demonstrated the superiority of N- terminal pro-BNP over procalcitonin and troponin to detect a complicated cardiovascular course either during the preoperative time or in the immediate postoperative phase. Kerbaul et al. [37] suggested that a patient with a preoperative NT pro-BNP level lower than 275 pg/ml has an excellent postoperative prognosis. The most important limitation of this study was the heterogeneous characteristic of the cardiovascular complications included in the design and the lack of measurement of the overall impact of the procedure on long-term mortality in this relatively small cohort of patients.

Previous studies have widely demonstrated in a nonelderly population that blood BNP dose is an excellent test to aid the diagnosis of heart failure in acute dyspnea, with a cutoff value for BNP of 100 pg/ml. Ray et al. [38] evaluated the predictive value of BNP in 308 patients older than 65 years since previous considerations suggest this value to be inadequate in the elderly: their BNP level is physiologically higher, and they generally show a progressive decrease in glomerular filtration rate (GFR). The authors found that 250 pg/ml is the best cutoff value in elderly patients (mean age 80 years; sensibility 78%, specificity 90%) in the emergency department. This study confirms that the measurement of BNP can help in the diagnosis of cardiogenic pulmonary edema particularly in elderly patients.

Inotropic and vasoactive agents

Metabolic effects

Metabolic disorders are frequently observed in intensive care patients consisting in hyperglycemia, hyperlactatemia, insulin resistance, rapid loss of lean body mass, increased plasma prolactin level, and inhibition of thyroid-stimulating hormone secretion. These metabolic disorders are often mediated by the endogenous sympathoadrenergic system and may be enhanced by the use of exogenous sympathomimetic drugs and particularly β_2-adrenoceptor agonists. Geisser et al. [39] examined 27 healthy male volunteers and compared the metabolic effects of dopexamine, a peripheral vasodilator with β_2-agonist properties, to those of fenoterol, a pure β_2-agonist. They demonstrated that, in contrast with fenoterol, dopexamine has no effect on carbohydrate metabolism (lack of variation in glucose plasma concentration and glucose clearance) and does not enhance gluconeogenesis. Its effects on fat and protein metabolism are comparable to those of fenoterol. The authors stated that this lack of effect on carbohydrate metabolite suggests that dopexamine exerts its hemodynamic effects more through DA_1 receptors than β_2-receptors. Moreover, the previously demonstrated clear relationship between strict control of plasma glucose and outcome in ICU patients suggests the use of dopexamine to increase cardiac output and splanchnic blood flow without enhancing carbohydrate metabolism.

In high-risk surgical patients Schilling et al. [40] compared the effects of dopexamine, dobutamine, and dopamine on prolactin and thyrotropin secretion on the first postoperative day. Using equipotent doses to obtain a 35% increase in cardiac output Schilling et al. [40] demonstrated in a prospective study including 30 male patients that dopexamine and dobutamine have no hypophysiotropic effects while dopamine suppresses prolactin and thyrotropin secretion. This effect disappeared with

dopamine withdrawal, suggesting that this vasoactive agent is associated with increased susceptibility to infections and hyper catabolism.

Hemodynamic effects

During septic shock the most important goal of the hemodynamic treatment is to restore mean arterial pressure with potent vasoconstrictive agents such as norepinephrine. The demonstration of a vasopressin deficiency in patients with septic shock provided the rationale for its use in patients with catecholamine-treated septic shock unable to attempt the adequate level of mean systemic arterial pressure. Morelli et al. [41] carried out a prospective open label study with IV bolus dose of terlipressin (1 mg) in 15 patients, and observed increased mean arterial pressure, gastric mucosal perfusion determined by laser-Doppler flowmetry technique, urine output, and creatinine clearance while decreasing cardiac output. An increase in the ratio of GMP/systemic oxygen delivery suggested a favorable redistribution of the perfusion to the gastric mucosa able to prevent splanchnic ischemia. By reducing the need for high-dose norepinephrine, terlipressin might avoid the conventional use of norepinephrine in septic shock without compromising organ perfusion.

Fluid resuscitation

Epidemiology

Fluid resuscitation is the primary goal in the hemodynamic management of patients with circulatory failure. However, it is still uncertain which solution is most suitable for fluid resuscitation in patients with sepsis with impaired oxygenation. Schortgen et al. [42] reported the results of an international survey aimed at evaluating the current choice of intravenous fluid for volume resuscitation among intensivists. The questionnaire was completed by 577 ICU physicians, and the results showed that colloids are widely used as first line (90%) most often in combination with crystalloids. Starches are the first colloid used in Europe, particularly in Germany and The Netherlands. Despite the recent literature about the potential indication for albumin in patients with cirrhosis, this study showed that the use of albumin is in decline.

Inflammatory process

Elderly patients undergoing major abdominal surgery appear to be prone to an elevated inflammatory response and endothelial injury which could affect their outcome. Boldt et al. [43] reported the effect of different volume replacement regimens on inflammation/endothelial activation in 66 patients aged over 65 years. This prospective randomized study demonstrated that the increase in the plasma levels of markers of inflammation (C-reactive protein, interleukin 6, interleukin 8) is higher with crystalloids than with a low molecular weight hydroxyethylstarch (130 kDa). Endothelial injury documented by adhesion molecules exploration (endothelial cell/leukocyte adhesion molecule 1, intercellular adhesion molecule 1) was higher after crystalloids than after hydroxyethylstarch administration.

Hemodynamic aspects

It is generally thought that fluid resuscitation augments cardiac function through an increase in preload (i.e., an increase in end-diastolic volume). However, recently published data suggest the potential role of a decrease in afterload following fluid resuscitation with colloids and crystalloids. Using echocardiography and phonomecanocardiography Kumar et al. [44] tested this hypothesis in 32 male healthy volunteers and found that the initial increase in stroke volume secondary to high volume saline infusion is associated with increases in load dependent but also load independent parameters of left ventricular contractility. The latter finding suggests that a decrease in blood viscosity reduced afterload (mainly end-systolic stress) and induced an increase in left ventricular contractility. This contribution was accompanied by an editorial by Nitenberg [45]

Excessive volume loading or increased capillary leakage may result in pulmonary edema, often referred to as extravascular lung water accumulation. Molnar et al. [46] compared the effects of fluid resuscitation with 4% modified fluid gelatin or 6% hydroxyethylstarch on hemodynamics and oxygenation in 30 patients with septic shock and acute injury. Using the PiCCO system the authors demonstrated that gelatin and hydroxyethylstarch cause similar short-term increases in cardiac index, oxygen delivery, intrathoracic blood volume index, without increasing lung water or worsening oxygenation.

Autonomic nervous system dysfunction

The decrease in heart rate variability which characterizes autonomic dysfunction and loss of autonomic balance occurs in sepsis and multiple-organ dysfunction syndrome and predicts an increase in the mortality of critically ill patients. Schmidt et al. [47] used a hyperoxic method to analyze cardiac chemoreflex sensitivity to test the autonomic balance in 40 patients suffering from the multiple-organ dysfunction syndrome. They demonstrated that the more the cardiac chemoreflex sensitivity is blunted, the more severe is the multiple-organ dysfunction syndrome,

without relationship to age, as has often been previously reported. However, the pathophysiological mechanism behind the altered cardiac chemoreflex sensitivity is not clear and requires further study.

Following a sting by a scorpion a direct stimulatory effect of the venom on the adrenals and on the sympathic nerves endings increases the secretion of endogenous catecholamines able to generate myocardial damage via coronary vasoconstriction and tachycardia. Balhoul et al. [48] reported the cases of six young patients (4–9 years) admitted for scorpion envenomation with myocardial damage demonstrated by myocardial perfusion scintigraphy coupled with radionuclide ventriculography and echocardiography. The authors also reported the regression of the abnormalities in two patients and suggested a relationship between severe scorpion envenomation and myocardial hypoperfusion.

Nutrition

Postpyloric feeding can enable enteral nutrition when gastric emptying is delayed. Many techniques have been described for blind placement of postpyloric tubes, but success is variable and alternatives require endoscopy or fluoroscopic screening. Stayt and colleagues [49] presented a method for tube placement that combines previously described techniques: pretreatment with 200 mg erythromycin intravenously, gastric insufflation with 500 ml air, monitoring by electrocardiography from the tip of the enteral feeding tube, and aspiration of fluid, testing for an alkaline pH. The tube used was 140 cm long, of 10 F, and had a weighted end (Viasys Healthcare Medsystems, USA). Postpyloric placement of this tube was successful at the first or second attempt in 35 of 40 patients (26 at the first attempt) with a mean Acute Physiology and Chronic Health Evaluation II score of 19±8.6 and a wide range of diagnoses. The median time required for tube insertion was 15 min (range 7–75). Alkaline aspirates were obtained during 32 attempted insertions; on 31 occasions the tube was in the small intestine. The authors conclude their multifaceted approach has a high success rate in a patient population in which postpyloric tube placement can be difficult.

Intravenous glutamine supplements appear to reduce infectious complications and length of hospital stay in ICU patients and may also reduce mortality, but the mechanism of benefit is unclear. Skeletal muscle has a central role in glutamine metabolism, and in critically ill patients muscle free glutamine concentrations can be only 25% of normal. A randomized blinded study by Tjader et al. [50] compared the effects of 0, 0.28, 0.57, and 0.86 g/kg body weight intravenous glutamine for 5 days as part of isocaloric, isonitrogenous total parenteral nutrition on plasma glutamine and muscle free glutamine concentrations. Intravenous glutamine supplements caused a dose related increase in plasma glutamine concentrations. However, muscle free glutamine and muscle protein synthesis rate was similar in controls and all the glutamine supplemented groups. Post-hoc analysis suggested the rate of muscle protein breakdown, assessed by armary 3-methylhistidine to be decreased by glutamine supplements. "Normalization" of plasma glutamine concentration is a plausible pathway for beneficial effects of supplements but not an effect on muscle.

Severe infection or hemorrhage are common terminal or near-terminal events in patients with severe cirrhosis. Either may prompt referral for intensive care. To determine the value of intensive care and intervention with mechanical ventilation Rabe et al. [51] retrospectively reviewed 76 consecutive cirrhotic patients referred to a tertiary ICU; 45 (59%) died in the ICU and 8 more during a median follow-up period of 94 days. The risk of death was related to the Child-Pugh score of severity in chronic liver disease (receiver operating characteristic area 0.87) but not the acute physiology component of the Acute Physiology and Chronic Health Evaluation II score. Over 80% of patients with a Child-Pugh score higher than 12 died in the ICU, patients with this severity of liver disease and severe infection doing particularly poorly. This information may guide admission decisions in patients with severe cirrhosis or inform advice on prognosis.

A study by van den Berghe and colleagues [52] focused intensive care physicians' attention on the potential benefits of maintaining euglycemia. To determine the effect that this has had on practice McMullin et al. [53] distributed a survey to ICU physicians and nurses in five Canadian university hospitals. None of the ICUs had an insulin or nutrition protocol. Several strategies were supported by over 60% of respondents as helping to achieve optimal glycemic control in critically ill patients: awareness of optimal glycemic control in general (83%), more effective "sliding scales" for insulin (80%), more research into glycemia control (77%), increased use of insulin infusions (70%), and more rapid laboratory results (61%). The median clinically important threshold for hypoglycemia was 4 mmol/l (interquartile range 3–4 mmol/l), and the median threshold for hyperglycemia in both diabetics and nondiabetics was 10 mmol/l. Just fewer than one-half of the respondents had concerns about the accuracy of glucometers. In this survey ICU practitioners did not consistently report application of a "euglycemic" approach in their practice. The issues identified will need to be addressed before this approach is more widely adopted.

To determine whether patient mortality is related to intensive care unit activity or staffed bed occupancy, Iapichino and colleagues [54] conducted a prospective study over 4 months in 89 ICUs from 12 European countries. A total of 12,615 patients were enrolled, 3,838 being defined as "high risk" by a Simplified Acute Physiology Score II higher than 32 and an ICU stay

longer than 47 h. Using stepwise logistic regression, mortality was found to be statistically significantly lower with greater ICU activity, although the effect was small. However, the relationship between "high-risk patient" activity and mortality was much greater: equivalent to a 19% decrease in ICU (17% decrease in hospital) mortality for every five additional "high-risk" patients treated per bed/year. There was also a relationship between ICU occupancy and mortality, occupancy above 80% in this database being associated with higher mortality—close to other estimates of 85% as ideal average bed occupancy for ICUs. The results support regionalization of intensive care with adequately sized and resourced ICUs.

Solid organ transplantation is limited by the availability of organ donors. A survey of hospital deaths by Opdam and Silvester [55] reviewed all hospital deaths occurring in 12 hospitals in Victoria, Australia, over 12 months. All hospitals had ICUs and seven neurosurgical services. Four trained researchers reviewed all 5,551 deaths. Predefined criteria identified 112 medically suitable potential organ donors. The medical records of all potential organ donors were reviewed by a panel of five ICU specialists. Among 69 patients with a formal diagnosis of brain death, organ donation was requested in 66. Consent to organ donation was confirmed in 39, 37 of whom became organ donors with two deteriorating before organ donation was possible. Forty-six additional patients had physiological support withdrawn before probable progression to meet "brain death" criteria within 72 h. The consent rate for organ donation and the missed potential donors are similar to other published findings. The authors suggest ongoing physiological support of patients likely to progress to meet criteria for brain death, and increasing consent rates, as strategies likely to increase organ donation.

Renal function and replacement

Acute renal failure (ARF) occurs in about 20% of critically ill patients. The exact timing of the diagnosis in a patient with gradual development of oliguria and slowly rising creatinine/urea values in the blood is difficult, and monitoring of renal blood flow (RBF) and glomerular filtration rate (GFR), if feasible and available, could help in this respect. Hence intensivists have searched for bedside techniques to monitor such renal variables and predict the occurrence and monitor the course of ARF. These efforts might also help to elucidate the pathogenesis of ARF in various clinical circumstances and thereby confirm or refute mechanisms demonstrated in animal models.

Swärd et al. [56] measured RBF and GFR in 17 non-oliguric postcardiac surgery patients by renal vein thermodilution as well as with the help of para-aminohippurate and ^{51}Cr-EDTA clearance techniques (via renal vein and in urinary samples). They compared results from thermodilution, blood (infusion) clearance, and urinary clearance via urine collections. Urinary clearance of para-aminohippurate was corrected for (variable and incomplete) renal extraction. The (constant) infusion technique and clearance calculated from determinations in arterial blood samples and infusion rates, compared to the standard clearance calculated from urinary samples and the renal vein thermodilution technique, was most reproducible and accurate. Hence the former method may help monitoring renal perfusion and function, even in oliguric patients, provided that renal para-aminohippurate extraction, which may vary widely, is known or correctly estimated, and a steady state of plasma concentrations has been achieved.

Renal replacement therapy, whether performed by intermittent or continuous techniques, is the treatment of choice for ARF in the intensive care unit. The therapy is not without hazards and complications. Some of the problems relate to the need for anticoagulation to keep the circuit and filter open, to the metabolic imbalances evoked by the (pre/postdilution) substitution fluids, and the optimal blood flow and ultrafiltration rate for clearance. Bollman et al. [57] compared bicarbonate with lactate buffer during hemodiafiltration in patients with multiple-organ failure, without liver dysfunction, in a cross-over study in eight patients and using the [^{3}C]lactate and [$^{2}H_2$]glucose infusion techniques. Arterial lactate concentration, glycemia, and glucose turnover were higher during lactate infusion because of the recycling of lactate to glucose. In these patients without liver function the lactate level rose to a mean of 3.3 vs. 1.7 mmol/l during bicarbonate hemodiafiltration. The buffers were equally effective in maintaining acid-base balance since metabolism of lactate yields bicarbonate. The authors concluded that (the cheaper) lactate-based solutions can be safely used, since lactate was rapidly cleared from the blood and either converted into glucose or oxidized. The latter increases metabolic demand, which may be disadvantageous in hemodynamically unstable patients, however.

Citrate is gaining popularity to replace lactate or bicarbonate in substitution fluids and to buffer acidemia. Citrate is converted to bicarbonate in the liver. Moreover, citrate infusion before the filter binds calcium and thereby prolongs clotting. This anticoagulant effect can be used to keep the filter open and to prolong its survival. Moreover, citrate might replace heparin or other methods of anticoagulation, which may have adverse effects. Along these lines, Monchi et al. [58] compared unfractionated heparin with regional citrate-based anticoagulation during continuous venovenous hemofiltration in a cross-over study in eight patients. Anticoagulation with the former was guided by the activated partial thromboplastin time (60–80 s). Indeed, filter survival was prolonged with the latter therapy, because of less frequent clotting, thereby saving

blood and thus blood transfusions. The filter also remained functional in spite of prolonged use (median 70 h with citrate). There was one episode of serious bleeding during heparin anticoagulation and one episode of serious metabolic alkalemia due to underfiltration of citrate, in spite of continuous post-filter calcium chloride infusion. This underscores the need for monitoring the citrate effect to prevent overdosing, with help of (total and ionized) calcium concentration determinations in the blood. Conversely, acid-base balance was better maintained with citrate than with heparin, in spite of postdilution bicarbonate-containing fluid substitution. Future studies may focus on morbidity of patients in a randomized controlled clinical trial.

Another measure to keep the circuit open is to guarantee adequate blood flow. Baldwin et al. [59] observed in 12 patients that unforeseen and transient diastolic blood flow reductions below the set diastolic blood flow rate of 83 ml/min (n=314) are associated with a shorter filter survival, independently of anticoagulation status. Blood flow was continuously monitored with a miniature Doppler device in this study and reductions could have resulted from catheter malfunctioning, among others. This study prompts for techniques to monitor, prevent or limit sudden blood flow reductions in the circuit.

In conclusion, the studies cited exemplify the continuing clinical need for determining more precisely the occurrence of ARF and refining renal replacement therapies.

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