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Year in review in Intensive Care Medicine, 2006. I. Experimental studies. Clinical studies: brain injury, renal failure and endocrinology

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Experimental studies

The "Experimental" studies, which were published both as original papers and in the form of brief communications, focused on three main subjects, i. e. improved techniques and side effects of mechanical ventilation, treatment of traumatic–hemorrhagic shock, and physiopathology and treatment of sepsis and septic shock.

Mechanical ventilation and lung injury

Experimental models of acute lung injury (ALI) have proved to be useful in achieving a better understanding of its pathogenesis and to test new ventilatory strategies. The type of lung injury model investigated, however, deeply influences the response to mechanical ventilation. In an interesting study, DiRocco et al. [1] investigated the alveolar mechanics in four different rat ALI models. ALI was induced by the detergent Tween-20, oleic acid, injurious mechanical ventilation, or endotoxin. Hypoxemia resulted in all four models. While significant alveolar instability was observed after Tween-20 and oleic acid treatment, as well as after injurious mechanical ventilation, this was not observed when rats were treated with endotoxin. It can be concluded that different pathogenic mechanisms induce hypoxemia, depending on the model used. The choice for ventilatory strategies should take this into account, particularly with respect to strategies aimed at stabilizing the alveoli.

Schreiber et al. [2] tested the effect of two different levels of PEEP in another rat model of ALI (unilateral hydrochloric acid instillation into the lung). This treatment induced hypoxemia, neutrophil recruitment and a marked cytokine response in the injured lung. The addition of 10 cm H_2O of PEEP ameliorated the arterial oxygenation and attenuated the inflammatory response in the injured lung without causing harm to the contralateral uninjured lung. Mechanical ventilation with zero end-expiratory pressure had the opposite effects. This model is reminiscent of the situation of aspiration pneumonitis in critically ill patients, frequently more pronounced in one lung. Although one should be cautious with direct translation of these findings to the clinical situation, it is reassuring that applying PEEP to these patients might be beneficial to the injured lung without having apparent deleterious (overstretching) effects on the uninjured lung.

Nielsen et al. [3] investigated the hemodynamic effects of lung recruitment maneuvers in porcine model of lavage-induced acute lung injury. Using echocardiography together with right heart catheterization, the authors elegantly demonstrated that such a recruitment maneuver compromised cardiac output concomitant with a fall in left ventricular end-diastolic volume, and hypervolemia allowed attenuation of this response. Regardless of the volemia, a marked right ventricular dysfunction affiliated with the lung recruitment was at least in part responsible for this finding. In a comparable model Bayle et al. [4] tried to evaluate a sigmoidal equation for the description of airway closure, either focusing on the inflection point as associated with the maximal increase of the compliance or as assessed by eyeballing,. The authors concluded that the sigmoidal equation provides neither the precise onset nor the completion of airway closure, but that the pressure at the maximal increase in compliance and the zero-volume intercept are fairly equivalent.

Tusman et al. [5] and Richard et al. [6] investigated two fairly different techniques, particularly with respect to their complexity and applicability for routine care, i. e. positron emission tomography and CO_2 expirography, for the assessment of lung collapse and alveolar recruitment with PEEP maneuvers during mechanical ventilation in swine. Both methods yielded this information, with the PET technique being, for obvious reasons, restrained to very specific conditions. These two papers were accompanied by a editorial comment by Calzia [7].

During long-term mechanical ventilation in healthy ewes, two different approaches were tested, dedicated to blockade of the buildup and elimination of mucus in the endotracheal tube, respectively, i. e. the "Mucus Slurper" and the "Mucus Shaver". The former, as described by Kolobow et al. [8], is an integral part of the endotracheal tube that automatically aspirates all mucus at the distal tube tip. Within 24 h of mechanical ventilation it rendered the tube lumen free of mucus without any safety concern, in particular with respect to the maintenance of airway pressures. Berra et al. [9] demonstrated that coating the endotracheal tube with silver sulfadiazine in polyurethane in combination with the use of a concentric inflatable silicone rubber with "shaving rings" completely inhibited both the accumulation of secretion and the colonization of the tube wall over 72 h of mechanical ventilation.

The role of continuous versus intermittent infusion of ceftazidime was investigated by Girardi et al. [10] in a porcine model of experimental *Pseudomonas aeruginosa* pneumonia. Clearly, continuous antibiotic infusion yielded markedly higher tissue drug concentrations, but this effect was not affiliated with a reduced bacteria load in the organ.

Finally, Morel et al. [11] tried to characterize the time course of acute pancreatitis-related lung injury, to reproduce a frequent clinical etiology of non-pulmonary ARDS. Pancreatitis was induced in rats by injection of taurocholic acid into the biliopancreatic duct, i. e. using a well-established model of rodent pancreatitis. While pancreatic injury persisted over 18 h, lung injury was only transient and normal pulmonary function had resumed by the end of the experiment.

Traumatic-hemorrhagic shock

In a rat model of brain injury induced by cortical contusion Thomale et al. [12] investigated the effects of early (immediately after the trauma) i. p. injection of high-dose *N*-acetylcysteine. Early treatment with this compound did not modify posttraumatic microcirculatory blood flow, intracranial pressure or tissue edema formation, and thus the authors added a further intriguing piece to the complicated puzzle of the use of this compound in critical illness. Roesner et al. [13] focused their interest on the role of poly-(ADP)-ribose-polymerase (PARP) in shock states. In a rat model of hemorrhagic shock and resuscitation pretreatment with the PARP inhibitor 5-aminoisoquinolone (5-AIQ) on hepatic microcirculation and liver function, 5-AIQ attenuated the intrahepatic leukocyte–endothelial interaction and thus improved both the tissue energy status (as assessed by NADH fluorescence) and liver excretory function. This study was accompanied by an editorial comment by Barth et al. [14] highlighting the current status of the use of this therapeutic approach as well as both putative safety issues and currently developed alternatives targeted to reduce peroxynitrite toxicity.

Sepsis and septic shock

Animal models of endotoxemia and whole bacteria-induced septic shock remain invaluable tools to test pathogenic hypotheses and evaluate novel therapies for sepsis. Evidence has accumulated recently indicating that mitochondria from vital tissues do not function properly during sepsis. Crouser at al. [15] analyzed the proteome of liver mitochondria in endotoxemic cats. Fourteen mitochondrial proteins were differentially expressed in cats challenged with endotoxin, compared with untreated controls. Among the proteins that were found to be upregulated in septic animals were enzymes from the urea cycle, the 60-kDa heat-shock protein (HSP60) and manganese superoxide dismutase. Conversely, HSP70, F_1-ATPase and enzyme-regulating lipid metabolism were found to be downregulated by the endotoxin treatment. The authors suggest that variations in the expression of these proteins may play a role in the liver mitochondrial dysfunction such as that observed during sepsis.

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) has been shown to be a reliable marker differentiating patients with ventilator-associated pneumonia (VAP) from those with other lung diseases in the ICU. Levels of sTREM-1 have also been shown to increase rather specifically in patients with sepsis. Giamarellos-Bourboulis et al. [16] measured sTREM-1 in a cohort of 90 patients with VAP, together with an array of pro- and anti-inflammatory cytokines. They observed that the levels of sTREM-1 followed those of IL-10, a classical anti-inflammatory mediator, the highest levels being measured in patients with VAP and septic shock. Persistent elevation of sTREM-1 was associated with poor outcome, as this has also been shown in critically ill patients with other inflammatory mediators, or markers such as procalcitonin. Gibot and Massin, in an accompanying editorial [17], reviewed the current experimental knowledge on sTREM-1, and discuss the possible mechanisms by which sTREM-1 could be an anti-inflammatory mediator induced during severe infections.

The activity of interleukin (IL)-13 – an anti-inflammatory cytokine principally secreted by T helper type 2 (TH2) cells – overlaps with that of IL-4. IL-13 has been implicated in several allergic and parasitic diseases. Sepsis is characterized by an inflammatory response that is shifting from a TH1 to a TH2 response, at least systemically. Elevated levels of IL-4 and IL-10, as well as decreased TNF/IL-10 ratios have been reported, participating in the monocyte deactivation observed in those patients. Socha et al. [18] have measured IL-13, tumor necrosis factor alpha (TNF) and cortisol in a small population of critically ill patients with a systemic inflammatory response syndrome (SIRS). Patients with SIRS had increased plasma IL-13 levels compared with controls, highest in the subset of patients with sepsis. Interestingly, the circadian rhythm of cortisol was lost in critically ill patients with SIRS, but maintained for IL-13. Further studies are necessary to determine the role of IL-13 in the inflammatory response during SIRS and sepsis. IL-10 is another TH2 cytokine with anti-inflammatory properties. IL-10 is elevated in plasma from patients with sepsis, and participates in the monocyte deactivation and in the immune suppression observed in such patients. Stanilova et al. [19] investigated the possible role of a polymorphism in the promoter region (–1082) of the IL-10 gene for the susceptibility of sepsis and the outcome in patients presenting with severe sepsis. They found that peripheral blood mononuclear cells from patients carrying AA alleles at this position of the IL-10 promoter produced less IL-10 when stimulated in vitro. These patients had an increased risk of developing sepsis. Conversely, the presence of one or two Gs at this position was associated with an increased ex vivo IL-10 production and increased mortality. These results add to the body of evidence that at least part of the susceptibility and the outcome of sepsis are genetically determined, and highlight the probable pathogenic role of the anti-inflammatory cytokine IL-10 in this condition.

Hauser et al. [20] addressed the question of whether the beneficial effects of the peroxisome proliferator-activated receptor (PPAR-γ) ligand and nuclear transcription factor (NF-κ B) inhibitor 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (PGJ_2), which had been described in short-term rodent models, could also be confirmed using a delayed post-treatment approach during long-term, hyperdynamic porcine endotoxemia. In contrast to encouraging

reports in the literature, they reported that PGJ_2 stabilized systemic hemodynamics but had no beneficial effects on organ function. The authors referred this finding to low tissue drug concentrations and the delayed treatment.

Peripheral consequences of sepsis

A clinically important aspect of the management of septic shock was addressed by Hummler et al. [21], who compared the accuracy of two different pulse oximetry devices in a hypodynamic model of septic shock induced by tracheal instillation of *E. coli* in rabbits. The authors confirmed that the pulse oximetry signal is markedly impaired in such shock states. In addition, they also showed that the so-called "perfusion index" is not a reliable marker to detect an increased risk of bias. In his editorial on this paper, Gehring [22] presented a detailed discussion on the pulse oximetry technology and thus explained the reasons for this latter finding, i. e. the fact that the perfusion index reflects changes of local blood volume rather than flow.

The response to tissue ischemia is largely unknown in patients with severe sepsis and septic shock. In an interesting clinical study, Parenik et al. [23] induced transient upper limb ischemia in hemodynamically stable ICU patients and healthy volunteers. They measured thenar muscle oxygenation using near-infrared spectroscopy (NIRS) before and during limb ischemia. The muscle oxygenation decreased less rapidly in patients with septic shock than in patients with severe sepsis or localized infections and in healthy subjects. Sepsis patients who corrected this "anomaly" during their ICU stay had a better outcome that those who did not. A significant correlation was found between the decreased rate of tissue hypoxemia after limb ischemia and the SOFA score. The mechanisms by which muscles rendered ischemic in patients with septic shock have a decreased rate of tissue hypoxia remain to be unraveled.

Significant neuromuscular weakness is a consistent finding in patients with severe sepsis and septic shock, both during their ICU stay and after discharge. Invalidating weakness frequently persists for many months after the sepsis episode. Eikermann et al. [24] performed a series of muscular and electrophysiological tests in patients with sepsis. These confirmed an important muscular weakness in patients with clinically diagnosed critical illness neuropathy (CIP), but also in half of the patients who did not bear this diagnosis. Interestingly, although muscular strength was usually severely impaired, these patients did not show signs of muscular fatigability. The investigators concluded that the decrease in muscular strength is probably due to sepsis-related myopathy or axonal neuropathy, rather than muscular atrophy.

Therapy of sepsis

In a hypodynamic model of septic shock in ewes challenged with live *E. coli*, Wan et al. [25] investigated the effect of high-dose physiologic saline on mesenteric, coronary and renal blood flow. Volume expansion increased cardiac output and thus also regional blood flow, which was affiliated with improved creatinine clearance and fractional Na excretion. This beneficial effect, however, was only transient. In normodynamic porcine endotoxemia, Knotzer et al. [26] showed that incremental arginine-vasopressin did not compromise jejunal microvascular perfusion and oxygenation beyond the effects of endotoxin per se. This important finding was commented upon in an editorial by Asfar et al. [27], who highlighted that the microvascular effects of this treatment differ depending on the underlying pathology and the volemia status.

The use of dopamine in sepsis remains controversial, in particular since the SOAP registry showed an increased mortality in patients with shock treated with this drug. Increasing evidence indicate that dopamine carries adverse hormonal effects such as decreased prolactin and growth hormone responses. Increased apoptosis of cells in lymphoid organs has also been well described during sepsis. Using a polymicrobial peritonitis and sepsis model in mice (cecal ligature and perforation, CLP), Oberbeck and colleagues [28] showed that dopamine infusion is associated increased apoptosis of splenocytes in septic mice. A decreased rate of lymphocyte proliferation and cytokine production was also observed in mice treated with dopamine. Last but not least, treatment with dopamine was associated with the worst survival rate in this CLP model. These data suggest that a possible deleterious effect of dopamine infusion in sepsis could be related, at least in part, to an immune dysfunction induced by this drug.

Clinical studies have established that non-selective inhibition of nitric oxide (NO) increased the mean arterial blood pressure in septic shock while worsening the function of vital organs and the outcome. Li et al. [29] tested a NO scavenger (iron III complex of diethylenetriaminepentaacetic acid, DTPA FeIII) in antibiotic-treated rats challenged with *E. coli*. This scavenger decreased systemic NO levels and blunted the systemic cytokine response and lung neutrophil recruitment. Similarly to what was observed with inhibitors of the NO synthetase, it also restored mean arterial blood pressure but decreased the survival rate. These results add to a large body of literature and raise concerns as to whether non-specific NO inhibitors should ever be used in patients with septic shock.

The administration of activated protein C (aPC, drotrecogin alfa recombinant) was associated with an improved survival rate in patients with severe sepsis and septic shock in the PROWESS trial. Of note, the delay for cardiovascular recovery was significantly shorter in patients treated with aPC. Favory et al. [30] showed that

in rats endotoxin infusion induces a depression of the myocardial systolic performance, associated with a reduction in the density of heart capillaries and a recruitment of neutrophils in the heart, as assessed by an increased myeloperoxidase activity in this tissue. The treatment of endotoxemic rats with aPC largely prevented the cardiovascular dysfunction in this model at the level of both the microcirculation and the myocardial contractile function. This was also associated with a blunted inflammatory and vasodilatory response, possibly induced by aPC in this model. These experimental data suggest that aPC may prevent heart microcirculation impairment and myocardial dysfunction during severe sepsis.

Finally, Imperatore et al. [31] addressed the question of whether hyperbaric oxygen (HBO) exposure could beneficially influence disseminated intravascular coagulation associated with zymosan injection in rats. HBO not only prevented the otherwise marked fall in blood pressure, but also considerably improved the alterations in the coagulatory state associated with zymosan. This article was accompanied by an editorial comment by Öter et al. [32].

Clinical studies

Brain injury

There have been many advances in many aspects of intensive care medicine, notably the reduction in mortality in ARDS, the reduction in mortality and improvement in functional recovery after traumatic brain injury; however, sedation practices appear to have lagged behind advances in multi-organ support and outcome. Significant morbidity results from poorly managed sedation and pain management in the intensive care unit (ICU), ranging from anxiety and depression to flashbacks, agoraphobia, eating disorders and post-traumatic stress disorder. Therefore, manuscripts considering sedation practices and recommendations to improve the way in which sedation is administered and delivered should be of considerable interest to the intensive care community. In the year 2006 there were a number of such reviews, assessments of depth of sedation/anesthesia monitors and assessment of the effect of the introduction of guidelines.

Egerod et al. [33] published the results of a Danish national survey which reflects the change in practice across the rest of Europe with a shift from benzodiazepines to propofol and from morphine to either fentanyl or, in the UK, alfentanil by continuous infusion. They did, however, note that more attention is required to assessment of sedation and this has been a common theme in other manuscripts. Samuelson et al. [34] identified significant morbidity associated with high doses of sedatives and analgesics resulting in delusional memories. They recommend the use of the MAAS scale as a useful tool for predicting delusional memories or actual memories of the intensive care admission. Martin et al. [35], in a German survey, identified that patients were generally more deeply sedated than intended by the specialist in all phases of the ICU stay. They concluded that this was due to poor uptake of sedation scales and clinical practice guidelines, and is probably compounded by lack of training in the use of such scales. A positive effect from better pain and sedation management is reduced stress to the patient and a reduction in post-ICU morbidity, and it might also be expected to reduce length of ICU stay. Elliott et al. [36] unfortunately could not demonstrate this using an algorithm-based sedation guideline, which resulted in no change in the duration of mechanical ventilation.

These clinically relevant manuscripts relating to sedative practice and outcome are matched by the pertinent papers on organ donation and, in particular, donor availability. Kompanje et al. [37] showed that the number of potential donors is declining but that a considerable number of potential controlled non-heart-beating donors exist. They also noted that the most common reason for failure to procure organs was relatives' refusal. Sanner et al. [38] identified many obstacles to organ donation, including the type of approach, ethical problems concerning the potential donor and the relatives, the competence of the staff requesting donation, variability in diagnosing total brain infarction and the lack of intensive care bed resources. They suggest a tailored effort in order to increase donation. Revelly et al. [39], however, underlined the fact that our current management of "terminal" patients with a long duration of the dying process and variability in the withdrawal process make procurement difficult. Earlier identification of patients who may not survive in whom withdrawal might be considered can allow forward planning. Rundgren et al. [40] used an amplitude-integrated EEG monitor to predict outcome after cardiac arrest and induced hypothermia. They showed that a continuous aEEG pattern at the time of normothermia was discriminative for regaining consciousness.

Clearly the principal aim of neurologic intensive care is to promote survival, and although many papers were devoted to identification, management and procurement of organs from potential donors, either through controlled non-heart-beating donation or following diagnosis of brain death, a number of important papers helped our understanding of the pathophysiology of acute brain injury. Through better understanding of the processes we ought to improve the delivery of our care and subsequently functional recovery. Sirgo et al. [41] identified an important genotype (4G/4G) that can increase the risk of thrombo-embolic neurological complications after cardiac surgery with cardio-pulmonary bypass. This polymorphism of the plasminogen activator inhibitor 1 gene is strongly associated with stroke or encephalopathy after cardiac surgery, and a future strategy may be screening elective surgical patients for this gene and others

to try and help stratify risk and better inform patients. Chieregato et al. [42] investigated the use of xenon CT and transcranial Doppler ultrasound in poor-grade or complicated aneurysmal subarachnoid hemorrhage patients having raised intracranial pressure that was managed aggressively. They showed in patients with elevated intracranial pressure that mean middle cerebral artery flow velocity or Lindegaard index does not help to detect critical CBF or elevated cerebral blood flow. A recent audit of outcome of all trauma victims in England and Wales highlighted the lack of improvement in mortality in traumatic brain injury in the last ten years. Traumatic brain injury patients were different from all other trauma victims and suggest we need to critically appraise our approach to this vulnerable population. Grande [43] published an up-to-date review of the Lund Concept. This was followed by an editorial article entitled "Lund Therapy – pathophysiology-based therapy or contrived over-interpretation of limited date?" by Andrews and Citerio [44, 45]. The Lund Therapy, like many other interventions for traumatic brain injury, has not been tested in a randomized controlled trial. However, the lack of improvement in outcome over the past 10 years suggests that we may need to think laterally and investigate perhaps some aspect(s) of Lund Therapy, as the outcomes from the series reported by Grande are very good. Leal-Noval et al. [46] investigated the impact of red cell transfusion on cerebral oxygenation after traumatic brain injury. Clinicians using the Licox monitor will be familiar with this intervention in the management of patients with low brain tissue $P0_2$ levels. The authors were able to show that there was a variable but prolonged increment in cerebral tissue oxygenation in patients with low hemoglobin transfused. Clearly *measurement* of brain tissue $P0_2$ is required to identify low values and titrate this intervention.

Berg et al. [47] investigated intravenous glutamine supplementation in brain trauma patients in an attempt to establish whether this increases cerebral glutamate concentration. Fortunately they were able to conclude that with clinically relevant doses of glutamine, cerebral glutamate is unaffected. Naredi et al. [48] examined the sympathetic activation and inflammatory response in patients following subarachnoid hemorrhage and showed pronounced activation in a manner similar to that identified following traumatic brain injury. The absence of a relationship between norepinephrine spillover to plasma and plasma levels of pro-inflammatory markers suggests lack of a quantitative link between the two processes, sympathetic activation and inflammation. Sympathetic activation is more long-lasting than the raised plasma levels of IL-6.

Inoue et al. [49] examined the effects of neuromuscular blockade on the bispectral index recording in moderately and deeply sedated patients in the ICU and examined cerebral hemodynamics. They showed that neuromuscular blockade in moderately sedated patients but not in deeply sedated patients altered this; however, cerebral hemodynamics were not affected by neuromuscular blockade at either depth of sedation.

Finally, organ support in patients with acute brain injury has been the subject of many investigations. Koutsoukou et al. [50] examined respiratory dynamics in head-injured patients managed with either a positive end-expiratory pressure of 8 cm H_20 or with zero PEEP (ZEEP). Not surprisingly, they found that on day 1 of mechanical ventilation patients exhibited normal respiratory mechanics but after 5 days of mechanical ventilation at ZEEP static elastance and minimal resistance had increased significantly, perhaps reflecting low lung volume injury. Although interesting, this study does not reflect clinical practice in the management of traumatic brain injury, where informed neuro-intensivists are well aware that PEEP is important in lung organ support and that this can be readily applied up to levels equal to ICP without causing brain swelling. This paper was commented on by Mascia [51], who gave an excellent overview of the benefits of PEEP in patients on mechanical ventilation but also emphasized the importance of the impact of brain-oriented therapies of non-neurologic systems and reminded us they should always be evaluated. A multi-organ clinical approach was recommended as an optimal way to achieve our aim of good global functional outcomes.

Acute renal failure

Acute renal failure (ARF) in the ICU often requires some type of renal replacement therapy, in Europe commonly done by continuous venovenous hemofiltration (CVVH). Timing and dosing of this therapy and the patient category most likely to benefit, however, remain relatively unclear [52, 53], although Ronco et al. suggested a filtration volume of at least 35 ml/kg, also in septic shock patients, in order to increase survival [52]. Both aspects, i. e. high versus low volume, and early versus late start of therapy, were addressed in *Intensive Care Medicine* in 2006. Even though the significant clearance of toxic inflammatory mediators by high-volume CVVH and its benefit for outcome of septic shock still has to be proven, cumulating evidence supports that undertreatment may indeed be harmful [54]. Results obtained by Piccini et al. [55] further corroborate the need for higher filtration volumes, when applied early. In a retrospective before-and-after study on septic shock patients, the effects of a change in filtration volume policies from a (prescribed) 20 ml/kg/h ($n = 40$ patients) in the case of ARF, which may be too low [52, 54], to a (prescribed) dose of 45 ml/kg/h ($n = 40$ patients) for 6 h, started within 12 h after ICU admission before full-blown ARF and followed by conventional dosing, were observed. The authors did not observe demographic or clinical differences between the groups. Nevertheless, morbidity and 28-day mortality were lower in the early

high-volume CVVH group (27.5% vs. 55%, $p < 0.05$). Patients in the latter cohort had improved hemodynamics and spent fewer days on ventilators and in the ICU. Delivered doses were 85% or more of prescribed (zero fluid balance). Since this is a retrospective study over an 8-year period, the level of evidence in supporting widespread application is still relatively low, as elaborated in the accompanying editorial [54]. A similar judgment may also apply to the paper by Cornejo et al. from Chile [56]. They prospectively studied 20 patients with refractory septic shock regarding the effects of a single session of 12 h high-volume hemofiltratiton (100 ml/kg/h) and noted decreased norepinephrine requirements and lactate levels in at least 11 responders and a significantly lower hospital mortality than predicted on the basis of APACHE scoring. There was no control group. Notwithstanding the shortcomings of these interesting papers, the basis for designing a large-scale multicenter study addressing early and high-volume CVVH as adjunctive treatment for septic shock is becoming firmer and firmer, and large-scale prospective multicenter studies are eagerly awaited [54]. On the other hand, the procedures described appear relatively safe and clinicians might judge it appropriate to start CVVH early and increase its filtration volume in otherwise hopeless cases. Of note, the prescribed and delivered filtration doses may become disparate when isovolemia is not maintained, when the mode of substitution, i. e. pre- or postdilution, is changed, or when downtime increases owing to bag or filter changes. This should be taken into account both in designing studies and in clinical practice.

Endocrinology

Since the landmark studies by Greet van den Berghe [57] on the mortality-lowering effects of intensive insulin therapy for even mild hyperglycemia in the critically ill surgical patient in particular, many investigators have tried to confirm these results, with, up to now, highly variable results. Indeed, large European multicenter studies were not able to demonstrate benefits of intensive insulin therapy, and the debate on the reasons for these disparities is ongoing. One of the underlying hypotheses is that hyperglycemia is detrimental and contributes to endothelial oxidative stress, dysfunction and organ failure, among others. Many critically ill patients develop such hyperglycemia either because of unnoticed diabetes or, more frequently and importantly, because of the stress of critical illness associated with release of gluconeogenetic hormones and insulin resistance. Conversely, hyperglycemia may also impair host response and neutrophil function and may thereby even protect against excessive inflammation, for instance that associated with bacteremia and acute respiratory distress syndrome. Indeed, some of these phenomena may explain the results obtained by Ligtenberg et al. [58]. These authors retrospectively investigated the prognostic significance of glycemia in a mixed medical and surgical ICU in the Netherlands and failed to identify an independent predictive value of mean glucose (as well as variations in glucose) for mortality among 1085 patients, on top of that by APACHE scoring. These findings contrast with those of many others and point up the need for more research on the mechanisms of the detrimental effects of hyperglycemia in the critically ill. In Australia and New Zealand, hyperglycemia or treatment with insulin was associated with mortality on the ICU, even independently of age and disease severity [59]. A major difference with the Dutch study was their low frequency of intensive insulin treatment and lower overall mortality. Apparently, the results of van den Berghe [57] had not yet convinced all Australian/New Zealand ICU directors! Nevertheless, the marker or mediator role of hyperglycemia remains unclear, although studies by van den Berghe suggest hyperglycemia is harmful rather than hyperinsulinemia being beneficial [57].

Another endocrinological controversy is the concept of relative adrenal insufficiency in the critically ill septic patient. One of the arguments in favor is that a flat circulating cortisol response to ACTH stimulation in septic shock patients is predictive for hemodynamic improvement by adrenal replacement doses of hydrocortisone. The retrospective study by Morel and coworkers [60] on 52 septic shock patients challenges this concept. Patients who improved upon treatment (56%) by a 50% decrease in vasopressor needs had similar baseline and t = 30/60 min rises in serum cortisol upon 250 μg ACTH intravenously as patients without improvement (and significantly worse survival). The question thus remains what the precise role of ACTH testing is, while the benefits of low-dose steroid therapy in this syndrome are perhaps undisputed. The next question is whether relative adrenal insufficiency is also (not) identifiable in other types of critical illness. Marik et al. [61] studied patients with acute or exacerbated chronic liver disease in the liver transplant ICU and identified 16 (of an initial 101 with normal ACTH test results) who, upon repeated testing with 1 μg ACTH intravenously, had a baseline and/or 30-min cortisol level below 550 nmol/l, suggestive of "adrenal exhaustion" and insufficient secretion. The latter was associated with low HDL cholesterol levels, the substrate for cortisol synthesis. The authors stress that repeat testing with ACTH may be necessary to evaluate changes in adrenal function in critical illness, even in non-septic patients. The clinical significance of these results remains unclear, however.

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