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SPECIAL ARTICLE

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Year in review in Intensive Care Medicine—2003

Part 3: Intensive care unit organization, scoring, quality of life, ethics, neonatal and pediatrics, and experimental

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Intensive care unit organization, scoring, quality of life, ethics

Outcome research in intensive care medicine has traditionally used hospital mortality as the primary endpoint of interest. There exists a broad consensus, however, that other outcomes are equally important. This is reflected in the growing number of studies focusing on long-term outcomes. In 2003, several studies aimed to assess the quality of life (QOL) of intensive care survivors. Halonen et al. [1] studied the health-related quality of life (HRQOL) in survivors of severe acute pancreatitis. Among their sample (245 patients from a surgical ICU), 13% of those who survived hospitalization died within the following years. HRQOL in survivors was, however, not different from a sample of the normal population, 87% even returned to work. Lizana et al. [2] conducted a prospective observational study in a mixed ICU. Comparing QOL with that before and after the ICU stay, patients more frequently reported worse QOL after the ICU for the domains of pain/discomfort and anxiety/depression than for physical domains. Factors commonly associated with a change in QOL were previous problems in the affected domains, prolonged hospital length of stay (LOS), greater disease severity at admission and also greater degree of organ dysfunction during ICU stay.

Kaarlola et al. [3] compared QOL 1 and 6 years after ICU discharge. In their sample of patients, the survival rate after 6 years was still lower than in the normal population. Although the health-related indices of QOL were worse compared with the normal population, 35% reported it to be better than before intensive care. In addition, physical and emotional dimensions seemed to improve differently, which could have implications for future QOL studies. Granja et al. [4] evaluated QOL of ARDS survivors. In their sample of 29 patients, the 6-month follow-up after ICU discharge revealed that 41% had normal lung function again. Among the other patients, lung function impairments were mild to moderate. Many patients had impairments only in carbon monoxide diffusion. The QOL of post-ARDS patients was similar to other ICU patients.

A Norvegian study, undertaken by Kvale et al. [5], evaluated the impact of a doctor-led outpatient follow-up clinic for former ICU patients. Of their patients (345), 183 living in the hospital's region were offered follow-up. More than 40% of these patients lost more than 10 kg body weight after their ICU stay. The authors thus concluded that nutritional status and weight loss constitutes a major concern after ICU stay and should be further investigated. Somme et al. [6] investigated the outcome of elderly ICU patients. In a population of patients aged 75 years or older, severity of illness at admission, but not age, was associated with ICU mortality. After ICU discharge, deaths occurred predominantly during the first 3 months: age and prior limitation of activities were associated with the risk of dying. Hofhuis et al. [7] studied whether the Short Form-36 questionnaire can be used to assess the patient's quality of life on admission to the ICU by use of proxies. They concluded that this was reliably possible, although proxies tended to underestimate the QOL of their relatives.

Besides the long-term outcome of our patients, the needs of family members have gained increasing attention. Heyland et al. [8] investigated the satisfaction of substitute decision-makers for ICU patients with decision making in the ICU. They found that most of them wanted to share the decision-making responsibility with physicians. Overall, however, they were satisfied with their decision-making experience. In addition, Azoulay et al. [9] investigated whether allowing family members to participate in the care of patients in intensive care units (ICUs) would improve the quality of their experience. Interestingly, only 33.4% of the family members wanted to participate in the care of their relatives, although 88.2% of the caregivers felt that participation in care should be offered to them.

Measurement of ICU performance still relies on risk-adjustment, which is achieved by the use of prediction models: by providing an estimate of mortality rate for a patient cohort after adjusting for severity of disease and case mix, they allow a hospital's performance to be compared to a "standard" in order to measure quality indirectly. Although widely used, the problems of the systems under use are well established. Beck et al. [10] aimed at an external validation of three prognostic models (SAPS II, APACHE II and III) in adult intensive care patients in South England. The external validation showed a similar pattern for all three models tested: good discrimination, but imperfect calibration, as has been previously reported. Glance et al. [11] investigated a new approach for model construction. Models obtained by customizing SAPS II using a non-hierarchical and a hierarchical approach both exhibited excellent agreement on the identity of ICU quality outliers.

External validation of the Multiple Organ Dysfunction (MOD) score was the goal of the study by Buckley et al. [12]. They investigated1,809 patients admitted to an ICU for more than 24 h over a 3-year period. They found that, in their population, the MOD score constituted a valid measure of multi-organ dysfunction.

During the past years, it has become more and more accepted that the organizational and functional characteristics of intensive care units might impact on outcome. Metnitz et al. [13] studied the prognosis and outcome of patients readmitted to 31 Austrian intensive care units (n=15,180). Readmitted patients (5.1%) exhibited a four-fold hospital mortality, compared to never readmitted patients. The results of their study provides evidence that there exists a group of patients at higher risk for readmission to the ICU: at the time of their first ICU discharge, these patients presented with residual organ dysfunctions,

which were associated with an increased risk for being readmitted. Optimizing organ functions in these patients before discharge from the ICU could result in reduced readmission rates.

A French single-center study [14] aimed to assess the appropriateness of ICU triage decisions. Garrouste-Orgeas concluded that refusal of ICU admission was—besides other factors—related to the ability of the triaging physician to examine the patient. Specific training of junior physicians in triaging might thus, according to this study, improve triage decisions. Iapichino et al. [15] studied the predictive ability of pre-illness and illness variables, impact of care and discharge variables on the post-intensive care mortality in 5,805 patients, treated with high intensity of care in 89 ICUs, who survived the ICU stay. Worse outcome was associated with the physiological reserve before admission to the ICU, type of illness, intensity of care required and the clinical stability and/or the grade of nursing dependence at discharge. Uusaro et al. [16] studied the effects of ICU admission and discharge times on mortality in 23,134 consecutive emergency admissions from 18 Finnish ICUs. In their study, weekend ICU admissions were associated with increased mortality, and patients in the ICU were found to be at increased risk of dying in the evening and during night time.

Azoulay et al. [17] report that several deaths of patients admitted to ICUs occur after a decision to forgo life-sustaining therapy (DFLST). In their analysis, DFLSTs remained independently associated with death after adjusting for comorbidities and severity at ICU admission and within the first ICU week. According to the authors, this highlights the need for further clarifying determinants of DFLSTs and for routinely collecting DFLSTs in studies with survival as the outcome variable of interest. An Italian multicenter study, conducted by Giannini et al. evaluated the attitudes of physicians in end-of-life decisions [18]. The results showed a tendency not to involve patients or their families, and also a very limited involvement of nurses. They concluded that, in addition to studies that determine current medical practice and its motivations in end-of-life situations, there is also a need for reflection about the ethical acceptability of medical practice.

The objective of the study by Stubbert et al. [19] was to determine types, sources and predictors of conflicts among patients with prolonged stay in the ICU. They investigated all patients admitted to the participating ICUs whose stays exceeded the 85th percentile (n=656). They identified 248 conflicts involving 209 patients; Disagreements over life-sustaining treatment and poor communication were found to be the major sources of conflicts. Paper documentation in the ICU is gradually being replaced by intensive care information systems. Bosman et al. [20] evaluated the effect of such a system on nursing activity. They reported that the use of an information system in patients after cardiothoracic surgery reduced the time needed for documentation and thus increased the time nurses had available for patient care.

Neonatal and pediatric intensive care medicine

Introduction

Why have a "Neonatal and Pediatric" section in *Intensive Care Medicine*? There are many reasons, but, chiefly, our mission is to provide a medium for communication and the exchange of current work in the field, which will also be of interest to our general readership. Unfortunately, over the course of a year, we are not able to group the publishing of articles on a similar theme which, although helpful for readers, would slow down publication times and meet with disapproval from our authors. Hence, we have seen the need to review for our readers the developments that have been presented in the journal over the last year. Some articles you may have missed. This editorial will provide a unique opportunity to see these and other articles in context and, hopefully, you will go back and read what has been presented. Alternatively, if your field of practice is not neonatal and pediatric—and perhaps this section is something you might overlook in your usual reading—we hope that you welcome this review by subject area. Our intention is to encourage "cross-fertilization" of the ideas and information that were reported in 2003.

Patient population, severity and administration of pediatric critical care service

Two aspects of providing pediatric intensive care (PIC) for health communities or populations — estimating the risk of mortality and classifying the cause of illness — were addressed by Slater et al . First, in association with the Paediatric Index of Mortality (PIM) study group, these authors provided a revised version of their mortality-prediction model — PIM2 — that now adjusts for widespread improvement in the outcome of PIC [21]. It should also be noted that PIM2 is now international, and is based on over 20,000 patient admissions from 14 units in Australia, New Zealand and the United Kingdom. Second, in collaboration with the Australia and New Zealand Paediatric Intensive Care Registry, the group reported an empirical system of diagnostic coding that hopefully should enable better inter-unit description of admissions [22].

On a similar theme, there were three reports on the significance of disease- or therapy-specific severity scoring. Kuppermann et al [23] highlighted for our readers the purpose and accuracy of diagnosis-specific severity scoring in their summary of the literature on meningo-

coccal septic shock. Lamas et al. [24] reviewed poor prognostic features in 151 blood or bone marrow transplant recipients. And, last, Anton et al. [25] suggested, in their review of 19 patients with acute respiratory distress syndrome (ARDS) necessitating high-frequency oscillatory ventilation (HFOV), that scores of respiratory failure were inadequate at assessing severity when using this modality.

Another aspect of PIC is centralization of services and the safe transport of the seriously ill to tertiary centers. Vos et al., in The Netherlands [26], reported the results of a postal survey completed by pediatricians working in community hospitals. They concluded that there was a need for specialist transport teams, not least because of the stress experienced by attendants and the risk of adverse events associated with their transfers. From South Africa, Hatherill et al. [27] provided data on 202 PIC transfers in a resource-limited setting. These authors found a high incidence of transfer-related adverse events, most commonly in transfers from non-academic metropolitan hospitals. Finally, Trevor Duke, who works in Victoria, Australia, succinctly reviewed this much neglected, and now 'global', issue [28].

Outcome of intensive care

Two reports covered different aspects of outcome of PIC. First, in regard to late outcomes after critical illness, Taylor et al. [29] evaluated functional outcome and quality of life some 3.5 years after admission in their series of 1,265 children. They reported that only 10.3% of the survivors had unfavorable outcomes and were likely to live dependent on care. In fact, the majority of the patients had favorable outcomes and were likely to lead independent existences. Second, in relation to centralization of services and access to PIC, Goh et al. [30] found that, in Malaysia, the short-term outcome in 131 children (compared with 215 'controls') was not affected by initial inaccessibility to intensive care providing the children finally received care in a tertiary center.

Respiratory mechanics, support and treatment

Since pulmonary function testing is central to describing and understanding pulmonary pathophysiology and therapy, Hammer et al. [31] undertook an important study of the methodology. These authors found, in a series of 10 intubated infants, that test inflation and deflation maneuvers affected subsequent measurements of respiratory system compliance but not measurements of maximal expiratory flow-volume relationships. Hence, they suggested that careful planning of this type of testing is necessary to ensure appropriate interpretation of any changes.

In regard to mechanical support, there were three reports. First, Huckstadt et al. [32] reported their prospective, randomized, cross-over clinical trial of two different continuous positive airway pressure (CPAP) systems in 20 infants. Within-subject comparisons of tidal breathing parameters of the two CPAP devices showed that, during the breathing cycle, the valveless Infant Flow System — in comparison with the Babylog 8000 — increased air flow and tidal volume with less fluctuations in CPAP pressures. Second, Plotz et al. [33] described how they used HFOV and conventional mechanical ventilation to ventilate independently the lungs of a 14-year-old girl with differential lung pathology. Last, Gregor et al. [34] tested, in an in vitro pediatric model, the delivery of aerosolized perfluorocarbons (PFC) during mechanical ventilation. The authors found that the type of PFC, size of endotracheal tube and ventilatory settings influenced the delivery of aerosolized PFC.

Surfactant has been the mainstay of neonatal pulmonary therapy for respiratory distress syndrome. Hilgendorff et al. [35] examined its role in an experimental model of meconium aspiration syndrome. Their principal finding, in addition to improvements in gas exchange, was that surfactant administration had a significant influence on the transcription of inflammatory cytokines in the lung. In children, Moller and coworkers in the Surfactant ARDS Study Group [36] reported the results of a randomized, multicenter study of bovine surfactant in severe ARDS. After studying 35 patients (20 received surfactant), the group concluded that treatment with surfactant provided only a short-term improvement in oxygenation.

Last, in two illustrative cases of plastic bronchitis, Noizet et al. [37] reminded us of the importance of endoscopic diagnosis and physical treatment, even in the very young child with life-threatening complications such as pneumomediastinum.

Cardiac assessment and postoperative cardiac critical care

Invasive cardiac output measurements are infrequently undertaken in children. Chew and Poelaert [38] therefore reviewed the accuracy and repeatability of Doppler measurements reported in 23 articles (representative of 629 children) published over the last 20 years. They concluded that this form of assessment is acceptably reproducible and is most useful when used to track changes.

In the congenital heart disease, cardiac surgical patient, risk of—or the presence of—pulmonary hypertension is important in planning postoperative care. Two papers addressed treatment with inhaled nitric oxide (iNO). Stocker et al. [39] reported the findings of a randomized trial of intravenous sildenafil in addition to iNO in 15 infants. They found that the intravenous phosphodiesterase inhibitor augmented the pulmonary vasodilator effects of iNO. However, this response was not without

risk, since sildenafil also produced systemic hypotension and impaired oxygenation. Hermon et al. [40] looked at the potential toxicity of iNO. They reviewed their treatment of 38 children who had received postoperative iNO in the range of 5–40 ppm and found that methemoglobin levels were safe and below 4%.

A third paper in the cardiac surgical population looked at the influence of continuous magnesium infusion on postoperative arrhythmias. Dittrich et al. [41] reported the results of a randomized trial in 121 children (66 receiving placebo) where they found that magnesium reduced the rate of arrhythmias (the 'number needed to treat' to avoid one child with arrhythmia is 8, with a 95% confidence interval of 4 to 200).

Resuscitation

Two articles covered possible complications of resuscitation in infants. Wald et al. [42] informed us that extreme care was needed in order to avoid inadvertent air embolism caused by intravenous injections during resuscitation. While Matturri et al. [43] reported an autopsy case of myofibrillar injury in the right sinoatrial area and uppermost ventricular septum where prolonged external cardiac massage (90 min) appeared to be the cause.

A further two articles covered special forms of resuscitation. Schroth et al. [44] reported their medical treatment of a child with severe envenomation by Vipera berus (the common European viper or adder). And Thiagarajan et al. [45] reported their prolonged mechanical support of a child with extracorporeal membrane oxygenation as a bridge to cardiac transplantation.

Sedation and analgesia

Critically ill children present with a broad spectrum of conditions and have different sedative and analgesic requirements. Providing the appropriate level of sedation requires careful administration and monitoring of the response. Courtman et al. [46] showed, in a series of 43 mechanically ventilated children, that Bispectral Index Scores (BIS) correlated with Comfort scores only to a moderate degree. As an adjunct to monitoring, BIS was able to discriminate between light and deep levels of sedation, but not between deep and very deep levels of sedation.

In regard to providing analgesia, neonates and infants are a particular concern. For example, as Bouwmeester et al. identified [47], "we still do not know the morphine doses that provide sufficient analgesia after major surgery". These authors went on to study pain scores, morphine metabolism and administration in 68 postoperative neonates. They concluded that, in comparison with older neonates, those younger than 7 days require significantly less morphine. Also, continuous infusion is as effective as intermittent bolus dosing and, last, that mechanical ventilation decreases morphine metabolism and clearance.

Sepsis and shock

A European database (ESPNIC ARDS, www.meb.uni-bonn.de/ards) was searched to identify whether, in young children, there was a male predominance in severe sepsis and ARDS, when this was contracted in the years before puberty. Bindl et al. [48] reported that the male-to-female ratio was higher in sepsis-related ARDS compared with non-sepsis-related ARDS, with the highest ratio in those between 1 and 12 months of age. The explanation and physiology underlying this phenomenon remain unclear.

In another report, Leclerc et al. [49] studied one component of the acute endocrinology of pediatric sepsis syndrome. In a series of 18 children with meningococcal septic shock (and 15 control children without shock) they found that admission vasopressin levels were elevated, appropriately, even in those who died.

Since cytokines and NO reduce the cytochrome P450 (CYP450) level and drug metabolizing activity, Carcillo et al. [50] explored whether sepsis in children influenced antipyrine-mediated drug metabolism — which is a marker of CYP450 activity. In their series of 51 children with sepsis, and 6 critically-ill children without sepsis, they found that those with sepsis had a twofold reduction in antipyrine clearance, which was also inversely correlated to circulating levels of inflammatory mediators. The authors concluded that there was an "urgent need to re-evaluate the use of standard drug dosage schedules in sepsis."

Hatherill et al. [51] examined the relationship between base excess (BE), hyperlactatemia, hyperchloremia, 'unmeasured' strong anions and mortality in 46 children with shock. They found in this prospective observational study that there was no association between the magnitude of metabolic acidosis — as quantified by the BE—and mortality. Rather, hyperlactatemia, and not elevation of 'unmeasured' anions was predictive of poor outcome.

Clinical pathophysiology

In the PIC population, in addition to life support, there is the potential opportunity to influence the time course of disease and outcome, but we do need to understand the underlying pathophysiological mechanisms responsible for critical illness better. To this end, the journal published two such reports. First, in relation to traumatic brain injury, which is a common cause of death and acquired disability in childhood, Chiaretti et al. [52] described acute cerebrospinal fluid and plasma levels of neurotrophic factors in 14 head-injured children, in

comparison with 12 controls. The pattern of findings they reported may be an early indicator of severe brain injury or even acute endogenous responses aimed at neuroprotection. Second, in newborns with rapidly progressive pulmonary hypertension, Hoehn et al. [53] provided biopsy evidence, from two cases, of compensatory induction of endothelial NO synthase synthesis specifically in endothelial cells of the pulmonary arterioles. Both research groups [52, 53] present their hypotheses in full in their accompanying discussions which, like everything else in the journal, are worth reading.

Experimental studies

Acute lung injury

Studies on mechanical ventilation, PEEP, partial liquid ventilation and other treatment modalities of acute lung injury made up 17 out of 38, e.g. 45%, of the experimental papers published in *Intensive Care Medicine* in 2003, and, hence, represent the most important contribution to this section of the journal in 2003.

Mechanical ventilation

Dr. Watremez et al. [54] described a new porcine model of stable, methacholine-induced bronchospasm titrated to yield a twofold rise in peak inspiratory pressure. The authors characterized this model, which replicates the pathophysiological characteristics of severe bronchospasm in humans, by assessing both lung mechanics (resistance, compliance, elastance, intrinsic PEEP) and pulmonary gas exchange using the multiple inert gas technique to compute ventilation/perfusion distributions (V_A/Q). Then they used this model to compare the effects of He/O_2 breathing with those of N_2/O_2: while He/O_2 clearly improved lung mechanics, and thus substantially reduced the work of breathing by about 1/4, it was affiliated with a marked deterioration of pulmonary gas exchange resulting in aggravated respiratory acidosis. This effect was mainly due to an increased contribution of hypoventilated lung areas as well as a more pronounced dispersion of the ventilation and blood flow distributions indicating a worsened V_A/Q mismatch. An editorial comment by E. Calzia et al. [55] accompanies these articles.

The group of Capdevilla et al. [56, 57] studied the effects of 48 h of volume-cycled mechanical ventilation (Vt 8 ml/kg, I:E 1:1.5, PEEP 2 cmH_2O, RR 60/min) on fiber distribution and morphology, contractile function, electron microscopic structure and mitochondrial respiration in rabbit diaphragm and intercostal muscles. The authors concluded that prolonged mechanical ventilation leads to respiratory muscle fatigue and promotes atrophy, at least in part related to mitochondrial uncoupling. These papers are accompanied by an editorial comment by R. Hering et al. [58]. Gayan-Ramirez et al. [59] subsequently investigated the question of whether 24 h of mechanical ventilation in anesthetized rats affects diaphragmatic function. Muscle fiber distribution as well as contractile force were reduced in both the groups of anesthetized rats: with and without mechanical ventilation, albeit the effect was more pronounced in the artificially ventilated animals. Strikingly, the reduction in muscle contraction correlated with a reduced IGF-I mRNA expression.

Both Caruso et al. [60] and Herrera et al. [61] addressed the question of tidal volume effects on the pulmonary inflammatory response in rats: the former showed that not only high (24 ml/kg) but also even low tidal volumes (6 ml/kg for 1 h, ZEEP) induced IL-1β mRNA. By contrast, the latter demonstrated that PEEP titration according to the lung pressure-volume curve, e.g. a PEEP level just above the lower inflection point, was associated with a marked reduction of lung cytokine release and morphologic injury, which ultimately resulted in improved survival. The question of whether PEEP increments (0, 7, 14, 21 cmH_2O) may affect extravascular lung water (EVLW) accumulation and alveolar recruitment, investigated by thermal-green dye double indicator dilution and computed tomography, respectively, was investigated in sheep after saline washout-induced lung injury by Luecke et al. [62]. The authors showed that the PEEP-related reduction in non-aerated lung volume correlated with the decrease in EVLW, while the total excess tissue volume was not influenced. Vreugdenhil et al. investigated the effect of mechanical ventilation with no PEEP (ZEEP) and 4 cmH_2O PEEP on heat shock protein 70 (HSP70) and pulmonary inflammatory cytokine expression in a model of lipopolysaccharide (LPS)-induced lung inflammation [63]. Among the 42 male Sprague-Dawley rats treated intratracheally with LPS, there was a significantly higher expression of HSP70 and IL-1beta mRNA in the lungs of the ZEEP group than in the PEEP group and non-ventilated controls. The authors propose that HSP70 expression protects the lung against ventilator-induced lung injury by decreasing cytokine transcription in the lung.

Adjunctive therapy of acute lung injury

Several other studies evaluated further therapeutic approaches to reduce pulmonary edema in acute lung injury. In a canine model of oleic acid-induced acute lung injury, Su et al. [64] demonstrated that early, isovolemic continuous hemofiltration markedly improved systemic and pulmonary hemodynamics and gas exchange and reduced cytokine release and lung edema formation, ultimately resulting in attenuated morphologic damage. In a similar model, Hubloue et al. [65] investigated the effects of the endothelin A and B receptor blocker bosentan on the

pulmonary vascular response to oleic acid injection: while pre-treatment prevented the increase in pulmonary vascular resistance, as assessed using the 'gold standard' of pressure-flow plot analyses, post-treatment after the establishment of pulmonary edema had no effect. By contrast, Stubbe et al. [66] showed, in chronically instrumented sheep challenged by subsequent exposure to *S. typhi* endotoxin and oleic acid injection, that inhaled NO not only led to attenuated pulmonary hypertension but also to reduction of EVLW as assessed by thermal-dye double indicator dilution, mainly due to a fall in microvascular hydrostatic pressure.

Given the putative therapeutic impact of estimating lung edema accumulation with commercially available indicator dilution techniques, Rossi et al. [67] concluded, from measurements in endotoxic pigs, that not all methods of quantifying EVLW are equally reliable: a molecular double-indicator dilution based on the assessment of the volumes of distribution of ICG and deuterium (^2H)-labeled H_2O did not detect the significant increase in EVLW, as measured by the gravimetric 'gold standard'. The authors suggested that the thermal-dye approach might be more appropriate given the faster dissipation of temperature changes when compared to the heavy water distribution. Lim et al. [68] and Tariq et al. [69] investigated the impact of hypothermia (27°C rectal temperature vs normothermia) as well as the role of the imidazole derivative fluconazol in rodent models of LPS- and fecal peritonitis-induced acute lung injury. Both groups showed that these two treatment modalities led to marked attenuation of the inflammatory mediator release as well as the morphologic damage, at least when instituted prior to the septic challenge.

Finally, a number of authors studied several aspects of partial liquid ventilation (PLV): Loer et al. [70] demonstrated, in healthy anesthetized dogs, that incremental PEEP levels (0, 5, 10 cmH_2O) at otherwise constant respiration parameters substantially increased the amount of fluorocarbons eliminated via evaporation, suggesting a particular impact of modification in the ventilator settings on the maintenance doses as well as instillation intervals during PLV. Cox et al. [71] underscored the fact that PLV might facilitate lung recruitment according to the paradigm "Open the lung and keep it open": in rabbits with saline lavage-induced lung injury, high frequency oscillation (HFO) with PLV at constant airway pressures improved CO_2 homeostasis and increased intrapulmonary gas volume, as derived from 3-dimensional reconstructions of computerized tomography imaging. Nevertheless, these beneficial effects of PLV may be counterbalanced by the impact of fluorocarbons on host defense: in *P. aeruginosa*-challenged rats bacterial phagocytosis by alveolar neutrophils was reduced resulting in impaired bacterial clearance.

Regional perfusion and metabolic alterations in shock

According to the paradigm of the "Gut as the motor of MOF" major importance is currently attributed to shock-induced alterations in hepato-splanchnic blood flow and metabolism, which was also reflected in a series of experimental studies. Most remarkably, in the vast majority of these papers data from investigations of large animal models were reported, thus underscoring the special attention paid to experiments using clinically relevant shock models. Using microdialysis for the determination of substrate concentrations in various organs, Klaus et al. [72] demonstrated that the endotoxin-related impairment of tissue metabolism in pigs was markedly attenuated when these animals had been 'preconditioned' by LPS injection a couple days before the experiment. An editorial by J.J. Tenhunen [73] accompanied this article. In a complex experimental setup in swine using multiple simultaneous flow measurements, Knuesel et al. [74] reported that the regional vascular and tissue CO_2 homeostasis—the latter assessed by mucosal tonometry—consistently reflected the changes in mesenteric, celiac and hepatic perfusion during controlled reduction of abdominal aortic blood flow. This study was accompanied by an editorial by D. De Backer [75].

Two papers dealt with the impact of catecholamine treatment on regional perfusion and metabolism. Giantamasso et al. investigated the effect of noradrenaline on various vascular beds in *E. coli*-challenged ewes. Similar to widespread clinical experience, this treatment improved cardiac performance and renal function and had no deleterious effects on any of the organ perfusion studied, e.g. cerebral, coronary and mesenteric blood flow. In endotoxic rats Levy et al. [76] investigated the mechanisms of hyperlactatemia affiliated with catecholamine treatment, i.e. infusing adrenaline or noradrenaline. The authors concluded that the well-known effect of adrenergic stimulation on carbohydrate metabolism rather than cellular hypoxia assumed importance in this context. K. Träger et al. [77] contributed a comment to this paper.

The ongoing discussion on the role of poly (ADP-ribose)-polymerase (PARP) in the pathophysiology of multi-organ failure was the subject of two contributions: in a long term (48 h) model of endotoxin-challenged sheep, Scharte et al. [78] showed that nicotinamide, when used as a PARP-inhibitor, was able to attenuate the derangements of cardiovascular function as well as to reduce the cholestasis resulting from LPS infusion. By contrast, other parameters of liver function were not affected by this treatment. As a logic extension of previously published studies on the respective individual interventions, Stehr et al. [79] investigated the therapeutic potential of combining the infusion of nicotinamide as a PARP-inhibitor with a highly selective blocker of the inducible isoform of the nitric oxide synthase (iNOS, 1400 W), during 24 h of porcine endotoxemia. Similar to

Scharte et al. [78] these authors also paid attention to integrating routine supportive measures, e.g. fluid administration, in a post-treatment experimental design. The combined treatment beneficially influenced the LPS-related disturbances of hepato-splanchnic energy metabolism, albeit some undesired effects of the high-dose nicotinamide infusion could not be excluded. These two papers were commented on in an editorial by C. Szabó.

Pittner et al. [80] tried to elucidate further the mechanisms of the improvement of small bowel mucosa acidosis affiliated with selective iNOS inhibition in porcine endotoxemia. Combining in vivo microcirculatory cinematography with quantification techniques (laser Doppler flowmetry and remission spectrophotometry to determine capillary hemoglobin oxygen saturation), the authors were able to replicate their previous findings that iNOS blockade indeed led to the blunting of the otherwise progressive development of ileal mucosal acidosis. According to their results, a redistribution of microvascular blood flow within the gut wall and/or a restoration of the NO-related reduction in regional mitochondrial respiration were potential mechanisms of this salutary effect. Finally, Dr. Bone's group also investigated putative side effects of infusing incremental doses of the vasopressin analog terlipressin to restore blood pressure in their ovine model of long-term hyperdynamic endotoxemia. The authors reported that the stabilization of systemic hemodynamics was associated with a marked pulmonary vasoconstriction. Strikingly, global oxygen uptake was also reduced, but the available data did not allow the drawing of a conclusion as to whether this effect was due to a fall in tissue oxygen demands or to the emergence of a pathologic oxygen demand/supply relationship. This paper was accompanied by an editorial comment from P. Asfar [81]. Finally, the question whether derangements of global metabolic homeostasis may reduce gastrointestinal motility via inhibition of vagal activity was addressed by Takahashi et al. [82] in anesthetized rats. Hyperglycemia was inversely related to the fall in vagal efferent spike count.

Basic mechanisms of organ dysfunction in inflammation

The interest of these studies focused on various aspects of the pathophysiology of organ failure including signal transduction and metabolic pathways. Thus, in rats injected with turpentine to create a regional, non-microbial inflammation, Osowska et al. [83] reported that parenteral nutrition enriched with cysteine-taurine-threonine-serine and glutamine led to attenuation of the disturbance in body protein metabolism. This finding further pointed to the concept of "nutriceutics" in intensive care, which was also raised by Ritter et al. [84], who investigated the relation of oxidative stress and outcome in a rodent model of polymicrobial septic shock resulting from cecal ligation and puncture. In order to mimic the clinical scenario, the animals received both fluid resuscitation and antibiotics. Lethal outcome was associated with not only more pronounced parameters of oxidative stress but also higher enzymatic antioxidant, e.g. superoxide dismutase and catalase activities, the latter presumably representing the organism's response to excess mitochondrial oxygen radical production. This paper was accompanied by an editorial from G. Albuszies [85] and U.B. Brückner.

Mohler et al. [86] underscored the importance of the appropriate choice of the microbial challenge for the investigation of inflammatory diseases: pulmonary inoculation of different strains of *S pneumoniae* in mice resulted in markedly different outcomes at 48 h of infection as well as in up to tenfold variations of lung cytokine release. The profile of cytokine formation, however, was not related to outcome. The role of signal transduction was investigated in two studies. Uchiyama et al. [87] established a dose-response curve of the 'designer crystalloid' ethyl-pyruvate in mice undergoing mesenteric ischemia reperfusion: a dose-dependent inhibition of the nuclear transcription factor NF-κB was associated with restoration of gut mucosal barrier function and, at the highest infusion rates, microvascular perfusion. A complementary study evaluated the impact of blocking the NF-κB activation in murine zymosan-induced organ failure using the unspecific anti-inflammatory compound pyrrolidine dithiocarbamate. Attenuation of both morphologic injury and biochemical parameters of organ damage was associated with a reduced expression on PARP, iNOS and leukocyte activation. This paper was commented on by U. Senftleben [88].

Brain function during systemic disease

Cerebral function is of steadily increasing interest in intensive care medicine and, hence, research papers focusing on this subject also contributed substantially to the experimental papers published in *Intensive Care Medicine* in 2003. Ohnesorge et al. [89] addressed the important question of using somatosensory evoked potentials (SEP) as a measure of cerebral dysfunction in a porcine model of acute pancreatitis induced by intraductal injection of Na-taurocholeate and enterokinase. SEP modifications were faster to emerge than EEG changes and systemic hemodynamic impairment. This article was accompanied by an editorial comment from S. Schraag [90]. In newborn piglets Zwiener et al. [91] showed that mechanical ventilation, when compared to spontaneous breathing, reduced the perfusion in different brain regions both at normoxic and moderately hypoxic arterial blood gases. In ewes Myburgh et al. [92] compared the effects of adrenaline, noradrenaline and dopamine on cerebral autoregulation, both in the awake state and during sedation with continuous i.v. propofol. The catecholamine infusion

reproducibly increased cerebral blood flow, an effect that was offset by the propofol administration. The awake and sedated states did not differ, however, with respect to blood flow regulation. Finally, Kuo et al. [93] studied the impact of resuscitation with hypertonic (3%) saline (HS) in rats with heatstroke-induced (42°C ambient temperature) shock, intracranial hypertension and cerebral ischemia. HS treatment markedly improved cerebral blood flow via an increase in cerebral perfusion pressure and thereby maintained both tissue oxygen content and cellular redox state.

Cardiac function

When compared to the previous years, the contribution of papers focusing on myocardial function during stress states has certainly decreased, which obviously reflects the redirection of research interests in general from studies of the systemic circulation to visceral organ perfusion and function. In isolated guinea pig hearts Behrend et al. [94] demonstrated that the Ca-sensitizer levosimendan attenuated the LPS-related impairment of both myocardial contractility and relaxation. Given that the improvement in heart function was similar both in sham and in LPS-exposed organs, the authors suggested that this compound did not act on the specific cardiac toxicity of LPS. In closed-chest pigs Kisch-Wedel et al. [95] compared the effects of i.v. adenosine, Na-nitroprusside and the stable prostacyclin analog iloprost on left ventricular function as assessed using a conductance catheter technique together with controlled preload variation by incremental inflation of a catheter placed into the inferior vena cava. Although a putative contribution of reflex activation of the sympathetic system could not be refuted, the authors concluded that iloprost has inherent positive inotropic properties. S.E. Ricksten [96] contributed an editorial comment to this paper.

Finally, Abroug et al. [97] tried to elucidate the pathophysiological mechanism of the vasoconstriction and left heart failure resulting from intoxication with the venom of the scorpion *Androctonus australis*. The scorpion venom massively increased endogenous catecholamine concentrations, and infusing the scorpion antivenom was only effective when administered simultaneously with the venom itself. Although this finding might question the effectiveness of the antivenom treatment, the usual subcutaneous inoculation nevertheless leaves a certain time window for its application.

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