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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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Outcome, ICU organization, scoring, quality of life, ethics

Outcome

Recent epidemiological studies have contributed important information to a better understanding of intensive care practice and the outcome of our patients. Garrouste-Ortegas et al. [1] examined the association between body mass index (BMI) and mortality in adult intensive care patients. They divided patients into four groups based on BMI. Although severity of illness at admission was similar between the groups, patients with a BMI lower than 18.5% experienced significantly higher ICU and hospital mortality rates. The authors concluded that BMI could thus be of importance in risk adjustment and recommend including it in the development of future scoring systems. Wunsch et al. [2] examined the association between day and time of ICU admission and hospital mortality in 102 ICUs in the United Kingdom. They found crude mortality rates to be higher for Saturday and Sunday admissions. After risk adjustment, however, mortality rates were not associated with differences in hospital mortality. Another United Kingdom study, this one by Harrison et al. [3], analyzed seasonal differences in the mortality of intensive care patients in ICUs. Winter was defined as the period from December to February and nonwinter, thus as the period from March to November. Crude hospital mortality rates were higher during winter. After adjustment for case-mix these differences disappeared. Unit occupancy and workload were not associated with the increased mortality. The excess winter mortality observed in ICUs in the United Kingdom, according to these authors, can thus be explained by variations in case mix and not by seasonal factors.

Outcome in older ICU patients

Boumendil et al. [4] studied prognostic indicators of long-term survival in 233 patients aged 80 years or more who were discharged from a medical ICU. Long-term survival rates were 59% at 2 months, 33% at 2 years, and 29% at 3 years. Multivariate analysis identified the presence of an underlying fatal disease and severe functional limitation as independent prognostic factors of death after discharge. The functional outcome, evaluated by the Instrumental Activities of Daily Living was excellent or good for 56% of the surviving patients. The authors concluded that long-term survival of ICU patients aged over 80 years was more related to the underlying conditions than to the usual prognostic factors.

To investigate the outcome of mechanically ventilated older patients, Esteban et al. [5] conducted an international prospective cohort study including 2,183 patients treated with mechanical ventilation for more than 12 h. They focused on patients older than 43 years of age, divided into two groups: those aged 43–70 years and those older than 70 years. Survival in hospital was 45% in those aged 43–70 year and 55% in those aged over 70 years. Variables associated with mortality in the elderly were acute renal failure, shock, Simplified Acute Physiology Score (SAPS) II and PaO_2/FIO_2 ratio less than 150. In contrast, the duration of mechanical ventilation, ICU stay, and hospital stay were similar to those in younger patients. The authors suggested that the decision as to admission to a medical ICU as well as the use of mechanical ventilation should be considered not solely on the basis of age, and requires selection of oldest patients on the basis of underlying medical conditions.

ICU organization

The organizational structure of health care facilities has been shown to affect outcome in critically ill patients in a variety of ways. Metnitz et al. [6] evaluated the association between structures, treatments, and outcomes in 31 Austrian intensive care units with more than 26,000 patients. ICUs were divided into three groups according to the size and function of the hospital: community hospitals and specialized trauma centers (group A), central referral hospitals (group B), and teaching hospitals (group C). Group C patients exhibited significantly higher risk-adjusted mortality. Although severity of illness at admission in groups B and C was similar, group C patients received significantly more invasive diagnostic and therapeutic interventions throughout their ICU stay. For several invasive interventions identified, odds ratios for group C vs. group B patients were significantly increased, even after adjustment for age, sex, severity of illness and reason for admission. Risk-adjusted multivariate analysis confirmed that six of these invasive interventions were independently associated with mortality. According to the authors, these results can be viewed from both an individual and an epidemiological perspective. In an attempt to achieve the best outcome for their patients (individual perspective) physicians often use a strategy to reduce the "maximum risk" as far as possible and therefore use available resources to whatever extent they think is necessary. In large hospitals more resources are available. Such a strategy may, on the other hand, increase the "average risk" (epidemiological perspective) and thus there may be a level of invasive treatment beyond which the associated risks outweigh the benefits.

Goldhill et al. [7] explored the relationship between hospital mortality and the time patients spent in the hospital before ICU admission. They found that both crude and risk-adjusted hospital mortality rates significantly increased with increasing hospital stay before ICU admission. The authors explain this with a higher degree of physiological derangement in patients with longer ward

stay before admission. The authors thus recommend the use of physiologically based early warning scores to identify patients at risk for intensive care admission since early recognition and intervention may potentially improve outcome in these patients. This issue was further highlighted in the study by Priestley et al. [8] who evaluated the effects of the introduction of a critical care outreach service on outcome. Their results provided evidence that outreach is able to reduce hospital mortality (odds ratio 0.52, 0.32–0.85) but may increase length of stay.

Distribution of resources among ICU patients is an issue of increasing importance. The need for intensive care rises with increasing age of the population but also with the increasing use of more invasive strategies in several kinds of diseases. At the same time available resources are becoming increasingly limited. Wasserfallen et al. [9] evaluated the impact of bed closure on patient outcome in a surgical ICU. Not surprisingly, SAPS II and occupancy rate increased during this period, as did readmission rate. ICU mortality, however, significantly decreased. Activities before and after the ICU did not change at all. The authors interpreted this as the result of the extreme flexibility of the health care system. They recommend implementing multiple indicators to be able to monitor the impact of external interventions. Jacobs et al. [10] reported on the economics of scale in ICUs and high dependency units in the United Kingdom. They found that unit size is significantly negatively associated with costs; the predicted average cost of a seven-bed unit is about 96% of that medicated for of a six-bed unit. Their analysis suggests that the cost situation in ICUs and combined units is to some degree changed by scale. They recommend considering this in the future design of ICUs. Einav et al. [11] investigated the attitudes of Israeli intensive care physicians concerning the triage of ICU patients. Israelis are both more likely to discharge one patient in order to admit another and less likely to admit new patients than their counterparts in the United States. The authors conclude that this may be related to the lack of ICU beds in Israel. Additionally, less compliance with admission may be related to alternative attitudes to resource distribution, based on personal ethics (differences in culture, religion) or practice.

Scoring

Risk adjustment between different or heterogeneous groups has become a standard of good research practice in intensive care medicine. Current systems, however, present a variety of problems, and thus much effort is invested in the refinement of available or development of new systems. Clermont et al. [12] tried to develop a predictive model to predict the temporal patterns of multiple outcomes, such as survival, organ dysfunction, and ICU length of stay from demographic variables and the profile of organ dysfunction at admission. Because such predictions cannot be constructed using standard methods, they used dynamic microsimulation, a technique suited to predict multiple events over time. The authors concluded that dynamic microsimulation can successfully predict the time course of multiple short-term outcomes and may thus prove practical as a prediction tool that evaluates ICU performance on additional dimensions in addition to the risk of death. Schellongowski et al. [13] compared three different severity of illness scores [Acute Physiology and Chronic Health Evaluation (APACHE) II, Mortality prediction model II, and SAPS II] and one specific score for cancer patients (ICU cancer mortality model, ICMM) for their prognostic performance in critically ill cancer patients. Their results showed that the three nonspecific scoring systems were equal to or better than the ICMM. The authors explain this with the fact that the ICMM was developed to account for cancer specific problems, which may, however, not be directly related to the prognosis of these patients. Nimgaonkar et al. [14] used artificial neural networks to develop a new risk adjustment system. They used the original 22 parameters from the APACHE II score to build two models: one containing all 22 initial variables, the other incorporating only those which provide the majority of information (n=15). Although they found that their neural network models outperformed the original APACHE II score, these results should be viewed skeptically; what they did was similar to a second-level customization of the original APACHE II score. It is likely that customization with a simple logistic regression methods would have yielded similar good results. Gusmao et al. [15] were interested to determine whether more experienced intensivists would better predict the outcome of patients than their younger colleagues. They divided their staff into three groups (junior, medium, and senior). Physicians were asked about predicted length of stay and outcome (about the patients they were responsible for) during the first 12 h of the patients stay on the ICU. Physicians generally underestimated mortality. Senior intensivists performed better than their less experienced counterparts. The aim of the study by Pyykko et al. [16] was to validate a newly developed scoring systems to assess nursing workload, the Intensive Care Nursing Scoring System (ICNSS). This system differs from others as it defines nursing workload in relation to existing health care problems and thus the associated work necessary to provide adequate care for these problems. The authors demonstrated that the nursing workload differed according to the type of admission. They concluded that the ICNSS could be useful in conjunction with the Therapeutic Intervention Scoring System to draw attention to specific patient-related health problems.

Quality of life

Lamer et al. [17] evaluated the quality of life in patients who were admitted to the ICU after surgical complications and compared them with a group of matched controls without complications. Overall the perceived quality of life was similar in the two groups 6 months after ICU discharge. The ICU group, however, showed significantly worse pain and physical impairment values. The authors thus recommend further investigation into whether early physiotherapy and aggressive pain management can improve outcome in these patients. Kaarlola et al. [18] compared the performance of two measures of the general health-related quality of life, the EQ-5D and the RAND-36 among critically ill patients, following up more than 1,000 patients admitted to their ICU. The two systems differ in their approach to the problem: the EQ-5D contains five questions and a visual analogue scale to score the overall perception of the health state. It is thus easy and quick to use. The RAND-36, on the other hand, contains 36 different questions (needs thus more effort), divided into eight different domains, which are summarized in two dimensions: the physical and the mental component summary. Although the authors found a good correlation between the two different systems, they not astonishingly concluded that the RAND-36 is better suited to assess a detailed health status. To define predictors for prolonged ICU stay after coronary artery bypass grafting was the aim of the study by Bucerius et al. [19]. They found 20 different variables being independently associated with a prolonged ICU stay. In addition, off-pump coronary artery bypass graft (CABG) and minimally invasive CABG were also significantly associated with a shorter ICU stay than conventional (on-pump) CABG. They suggested that off-pump CABG should be more often used to decrease ICU length of stay.

Psychological problems and communication in the ICU

Communication, satisfaction, posttraumatic stress disorder

The particular nature of the work in the ICU explains why it may have important consequences not only for patients but also for family of staff members. Providing good communication and having difficult decisions accepted by all is an important element to prevent from the occurrence of conflicts within this large group of people. Griffith et al. [20] tried to evaluate the degree of satisfaction of clinicians (including physicians and nurses) regarding treatment plans taken for critically ill patients (mechanical ventilation, inotropes and dialysis). If uncomfortable, clinicians stated whether the plan was too technologically intense (the provision of too many life support modalities or the provision of any modality for too long) or not intense enough, and why. In 13 medical-surgical ICUs in four countries 657 mechanically ventilated adult patients were studied. At least one clinician was uncomfortable at least once for 43.1% of patients, primarily because plans were too technologically intense rather than not intense enough (93.9% vs. 6.1%, $p<0.001$). Discomfort was experienced mostly by nurses and was more likely for older, severely ill medical patients, those with acute renal failure, and patients lacking plans to forgo reintubation and ventilation. The authors conclude that acknowledging the sources of discomfort could improve communication and decision making. Myhren et al. [21] prospectively assessed the satisfaction in regard to information, support, and facilities of relatives of 50 patients who survived at least 6 days in the ICU and of relatives of 18 nonsurvivors in the ICU and compared this with the staff's expectations on these issues. They found that the relatives' satisfaction was greater than anticipated by the staff. Relatives were very satisfied with the support and communication in the ICU despite substantial distress, and relatives of survivors and nonsurvivors were equally satisfied.

Whatever the reasons, the experience of the patient relative to his/her stay in the ICU may be less than optimal. Cuthbertson et al. [22] tried to determine the incidence and severity of symptoms related to the diagnosis of posttraumatic stress disorder (PTSD) in a cohort of 78 survivors from a general ICU, all contacted at 3 months after discharge. They found a high incidence of symptoms consistent with PTSD, with 14% of patients meeting all criteria for this syndrome. This was associated with younger patients and those who visited their general practitioner or a mental health professional complaining of psychological symptoms. Such symptoms of psychological distress can also be present among family members, and this important aspect was studied by Jones et al. [23]. In this very elegant study the authors assessed the psychological recovery of relatives by examining the rate of depression, anxiety, and PTSD-related symptoms within 6 months after ICU. The closest family members of 104 patients recovering ICU were randomized to participate or not in a rehabilitation program 1 week after ICU discharge. The program comprised a 6-week self-help manual containing information about recovery from ICU, psychological information, and practical advice. The authors found a high incidence of psychological distress in many relatives. The written program concerning recovery from ICU provided to the patient and close relatives did not reduce this. High levels of psychological distress in patients were found to be correlated with high levels in relatives.

Delirium

The optimal management of patients developing delirium in the ICU is today a subject of major concern. Whether an optimal pharmacological strategy would improve outcome is unknown but is a key question for today intensivists. Skobrik et al. [24] compared olanzapine and haloperidol in such patients in a randomized trial. The delirium index decreased over time in both groups. Both the administered dose of benzodiazepines and clinical improvement was similar in the two treatment arms. No side effects were noted in the olanzapine group whereas the use of haloperidol was associated with extrapyramidal side effects. The new drug tested is thus an interesting alternative and may be of particular interest in patients in whom haloperidol is contraindicated. One clinical presentation of delirium in the ICU is agitation. Woods et al. [25] examined the frequency, characteristics, and outcomes of severe agitation among 143 mechanically ventilated medical intensive care unit patients enrolled over slightly more than 4 months. Twenty-three (16.1%) of them exhibited severe agitation as assessed by the Motor Activity Assessment Scale (MAAS) and sedative and/or narcotic doses above the established sedation and analgesia protocol or a combination of two or more sedatives. Interestingly, it was associated with adverse events including longer ICU stays, duration of mechanical ventilation, and self-extubation.

Ethics

The issue of withholding and withdrawing life-support therapy in emergency departments has rarely been addressed. Le Conte et al. [26] prospectively identified such clinical situations and the modalities and the criteria used by physicians to justify their decisions. Among all admitted patients 119 nontrauma patients (0.8%) were identified in whom a decision to withhold or withdraw life-sustaining treatments was taken. Resuscitation procedures were instituted for 96 patients (80%) before the decision was taken. This was particularly in elderly patients with underlying chronic cardiopulmonary disease or metastatic cancer. The patient's family was involved in the decision-making process in 72% of cases. In a related editorial Girbes [27] recommended that guidelines also take this aspect into account, thereby helping not only to save costly resources but also to prevent unnecessary human suffering.

Immunity and hemodynamics during sepsis

Sepsis and immune monitoring

While neutrophils are essential for host defense in infection, they are also important in the process leading to multiorgan failure in septic shock. Understanding the molecular mechanisms responsible for neutrophil leukocyte recruitment following a septic insult is central in developing strategies to limit the adverse effects of acute inflammation. In 15 patients with septic shock Chishti et al. [28] tested the hypothesis that neutrophil chemotaxis to interleukin (IL) 8 is reduced in septic shock. Flow cytometric measurements of chemokine and β-integrin surface expression were assessed for 5 days. Surface expression of neutrophil CXC chemokine receptors (CXCR1 and CXCR2) and the adhesion molecule CD11b were also examined, and associations between disease severity, gas exchange, and receptor expression were studied. Septic patients were compared to eight healthy controls. Surface expression of the chemokine receptor CXCR2 and the β-integrin CD11b, but not CXCR1, was reduced on neutrophils isolated from patients with septic shock compared with healthy controls. Chemotaxis to IL-8 was also lower in neutrophils from septic patients than those from healthy controls. The changes in receptor expression were correlated with measures of disease severity.

Reduction in the surface expression of CXCR2 with an increase in circulating IL-8 levels suggest that the reduced chemotaxis is mediated by receptor downregulation. Chemokine receptor antagonists are being developed and may be candidates for clinical trials in septic shock. This study suggests that these agents may not be effective in established, severe sepsis as chemokine receptor expression is already downregulated on circulating neutrophils and motility reduced.

There is no general agreement on the definition of "immunoparalysis," which is considered to occur during sepsis as the result of an imbalance between the pro- and anti-inflammatory reactions triggered by infection during the acute phase of the systemic inflammatory response syndrome (SIRS). Acquired "immunoparalysis" may be a risk factor for secondary infections and could contribute to the late mortality. The assessment of the immunological status of critically ill patients will become increasingly important in the near future with the development of immunomodulatory therapies. There is therefore a need for the development of new laboratory tests to assess the immune competence of critically ill patients. These tests should ideally reflect leukocyte responsiveness to bacterial products.

In 21 patients with septic shock and 11 volunteers Fumeaux et al. [29] showed that isolated septic monocytes and granulocytes have nonstimulated intracellular cytokine tumor necrosis factor (TNF) concentrations

lower than those measured in volunteers and were severely hyporesponsive to lipopolysaccharide (LPS). These phenotypic changes were correlated with disease severity and could be reproduced by treatment of normal leukocytes with plasma from patients with septic shock. For the authors, intracellular cytokine staining is a simple and rapid method to assess in situ and "on-line" the inflammatory balance and responsiveness of leukocyte subpopulations and could therefore offer a useful monitoring tool to assess the immune competence of critically ill patients. This study identified the cellular source of cytokines in whole blood and confirmed prior reports showing that septic phagocytes are characterized by a predominant anti-inflammatory phenotype, with hyporesponsiveness to LPS, depending on a plasma deactivation factor.

Excess of apoptosis has been identified in experimental septic shock as a cause of "immunoparalysis." Apoptosis is known to be regulated by two major pathways: the first involving the superfamily of TNF receptor members and the second under the control of the B cell lymphoma 2 (Bcl-2) gene family members, with either pro- or antiapoptotic functions. Corresponding levels of expression of the proapoptotic protein Bax and the antiapoptotic protein Bcl-2 is a regulation system for cell survival following an apoptotic stimulus. The Bcl-2/Bax rheostat may therefore become a new target for therapeutic interventions.

Bibault et al. [30] assessed the levels of expression of the antiapoptotic gene Bcl-2 and the proapoptotic gene Bax in circulating mononuclear cells (CMNC) harvested during the course of severe sepsis in formerly nonimmunocompromised patients undergoing hospital-acquired infection, in parallel to cytokine levels. A total of 24 patients without immunodeficiency undergoing standard goal-directed therapy for nosocomial sepsis, ten critically ill patients without sepsis, and ten healthy controls were included. Severe sepsis patients displayed increased cytokine concentrations, TNF-α being significantly increased at full-blown sepsis. Within 12 h after onset of infection lymphocyte counts were lower in severe sepsis patients than in critically ill controls, and this phenomenon was pronounced in $CD4^+$ and $CD8^+$ subsets. This was associated with enhanced apoptosis in CMNC and a significant down-expression of the Bcl-2 gene throughout the study. In contrast, the expression of Bax did not change significantly. Within 12 h after fever onset nonsurvivors expressed a tenfold downexpression of Bcl-2 compared to survivors.

Deterioration in immune response is measured by reduction in expression of HLA-DR on monocytes or ex vivo LPS-induced TNF-α production. The further influence of secondary surgery after severe injury on the immune response remains unresolved. Flohe et al. [31] studied the effect of surgical intervention in the immune response of severely injured patients. Sixteen severely injured patients with an Injury Severity Score higher than 25 points were included on day 1 after trauma and immediately before secondary surgery. The authors observed that mean fluorescence intensity of HLA-DR expression on monocytes and TNF-α ex vivo synthesis was significantly lower than in healthy donors. Overall, surgical intervention during the second week after trauma caused no further reduction in HLA-DR expression on monocytes or in ex vivo TNF-α synthesis. However, major surgery such as intramedullary nailing or pelvic osteosynthesis caused reduction in the HLA-DR expression and TNF-α synthesis, whereas minor surgical interventions such as osteosynthesis on peripheral joints exhibited no significant effects on immune response. Surgical intervention performed to clear septic foci normalized immune response by elevating HLA-DR expression on monocytes and ex vivo TNF-α synthesis. Severe injury caused elevated serum IL-10 levels whereas secondary surgery did not induce a further increase. This study showed that both initial trauma and major secondary surgery causes a suppression of immune functions, whereas minor secondary surgery does not lead to significant immune disturbance.

Genetic variability in host immune response is another major factor. With increasing mortality and morbidity, costs due to antibiotic-resistant bacteria, a better understanding of how host genetic variation affects resistance to specific infections is vital to develop new therapeutic and preventative strategies. Heat shock proteins (HSP) are thought to play a key role in this immune response. HSP are cytoprotective molecules expressed in response to a variety of stressful stimuli including heat, microbial infections, ischemia, and inflammatory mediators (e.g., cytokines).

Temple et al. [32] aimed at identifying a functional polymorphic site within HSPA1A and HSPA1B, which are in linkage disequilibrium with the silent mutation HSPA1B1267A>G and may explain its association with septic shock. The promoter region of HSPA1A and HSPA1B was sequenced in 100 healthy whites. Stimulation experiments were performed on 36 healthy subjects. It has been observed that HSPA1B-179C>T is in linkage disequilibrium with HSPA1B1267A>G and is associated with variable production of HSPA1B and HSPA1A. For the authors this suggested that HSPA1B-179C>T affects HSP70 production and may be a key determinant of individual susceptibility to a variety of infectious and inflammatory diseases.

Upregulation of the expression of membrane-bound forms of adhesion molecules on activated leukocytes and their corresponding ligands on endothelial cells is induced by inflammatory mediators such as TNF and IL-1β. Soluble isoforms of adhesion molecules shed from the surface of activated cells can be quantified in biological fluids allowing insights into early events of leukocyte recruitment.

Megarbane et al. [33] designed a study to compare cerebrospinal fluid (CSF) concentrations of adhesion molecules and to evaluate whether they originate from passive diffusion through damaged blood–CSF barrier or from local production in 19 patients with meningitis and 41 patients with sepsis or SIRS without cerebrospinal infection admitted consecutively to the critical care unit over an 18-month period. Serum concentrations of soluble adhesion molecules and cytokines were increased in the two groups, without significant differences. The CSF concentrations were elevated in both cases, whereas patients with meningitis demonstrated significantly higher CSF concentrations of soluble intercellular adhesion molecule (ICAM) 1, vascular cell adhesion molecule (VCAM) 1, E-selectin, and TNF-α, with higher corresponding CSF/serum ratios. Correlations between CSF and serum concentrations were found only in meningitis. These correlations were strong for soluble ICAM-1 and E-selectin but weaker for VCAM-1. VCAM-1 CSF/serum ratios were higher than ICAM-1 and E-selectin CSF/serum ratios despite similar molecular weights. Serum and CSF levels of cytokines and adhesion molecules were not predictive of death in the overall population, except that concentrations of ICAM-1 were significantly higher in nonsurviving patients. The authors concluded that the presence in meningitis of a discrepancy of CSF/serum ratios for molecules of the same molecular weight suggest intrathecal shedding in addition to diffusion through blood–CSF barrier.

It has become evident from several studies that antibiotics themselves may lead to enhanced endotoxin release and clinical deterioration. Antibiotics such as cephalosporins show a high endotoxin release with a consecutive cytokine release such as TNF-α liberation. Eggers et al. [34] investigated antibiotic-mediated release of TNF-α and norharman (an inhibitor of indolamine-2,3-dioxygenase with neuroprotective functions) in patients with hospital-acquired pneumonia with and without additional septic encephalopathy. TNF-α activates indolamine-2,3-dioxygenase with neurotoxic quinolinic acid as the end product. Norharman seems to counteract this mechanism and to play a role in neuroprotection. Thirty-seven patients were consecutively included (9 with hospital-acquired pneumonia, 11 with hospital-acquired pneumonia and septic encephalopathy, and 17 control patients). Blood samples were taken before, immediately after, and 4 h after administration of cephalosporins. Of the pneumonia patients 55% developed septic encephalopathy. ICU stay, complications, and mortality were significantly increased. A higher release of TNF-α after antibiotics was seen immediately in all pneumonia patients than in controls, whereas the level did not differ between patients with and without septic encephalopathy. Norharman was significantly increased in pneumonia patients 4 h after antibiotic treatment; there was a trend to greater enhancement in the pneumonia patients without encephalopathy. Patients with hospital-acquired pneumonia and septic encephalopathy had a significantly longer ICU stay with higher mortality rate than patients with hospital-acquired pneumonia alone. Further studies must investigate the interactions of neurotransmitters and cytokines in critically ill patients under different antibiotic therapies.

Sepsis and regional hemodynamics

Although volume infusion is considered an essential step in the initial resuscitation of septic patients, the ideal endpoints remain controversial. An important question is whether gastric tonometry (present the only means to assess tissue perfusion at the bedside on a routine basis) could help to guide fluid administration in severe sepsis. In a short-term interventional study Silva et al. [35] determined the effects of fluid challenge on systemic hemodynamic variables and gastric intramucosal partial pressure of carbon dioxide (PCO_2) in 24 adult patients requiring volume replacement. All patients were studied within 24 h after onset of severe sepsis or septic shock. A 6% hydroxyethyl starch solution (500 ml) was administered in 30 min. Complete hemodynamic data, blood samples, and gastric mucosal PCO_2 (automatic gas capnometry) were measured at baseline and 15 min after the end of fluid infusion. After fluid challenge the cardiac index increased from 3.8 l/min^{-1} m^{-2} (range 2.9–4.2) to 4.2 (range 3.1–4.9). The PCO_2 gap decreased from 9.8 mmHg (range 6.9–26.0) to 8.5 (range 6.6–17.4). Important individual variations were observed. The authors failed to observe significant relationships between changes in cardiac index and in PCO_2 gap, or between indices of preload (pulmonary artery occluded pressure, right atrial pressure, and pulse pressure variations) and changes in PCO_2 gap. In addition, changes in the PCO_2 gap and in (v-a)PCO_2 were not related; however, changes in the PCO_2 gap were related to baseline PCO_2 gap, positive end-expiratory pressure (PEEP), and cumulative doses of vasopressors. The authors concluded that the effects of fluid challenge on gastric mucosal PCO_2 are variable and related to baseline PCO_2 gap rather than to systemic variables. They observed that in general rapid volume infusion decreases PCO_2 gap, but this effect was more pronounced in patients with presumably impaired mucosal perfusion. This study clearly reminds that effect of fluid loading on tissue perfusion cannot be predicted from changes in cardiac output and oxygen delivery.

Pediatric and neonatal critical care

In the field of pediatric and neonatal critical care *Intensive Care Medicine* has had another productive year. Four topics have been featured—mechanical ventilation, in-

fection, organization and outcome, and hematology—and these as well as the other reports are discussed below.

Mechanical ventilation

In common with adult intensive care many researchers have focused on aspects of mechanical ventilation. Farias et al. [36] reported the findings from a multicenter international study that prospectively evaluated the daily practice of mechanical ventilation in pediatric intensive care units (PICU). Studying 36 PICUs for the 2-month period from April to May 1999, the authors found that one in every three patients required ventilatory support. In these patients nearly one-half of the total time of mechanical ventilation was devoted to weaning from support. An accompanying editorial [37] presented these data in a broader context and compared them with the recent data from the Pediatric Acute Lung Injury and Sepsis Investigators' Network [38]. The essential message is that more studies need to be carried out that describe "standard care" and justify our mechanical ventilatory strategies. To this end three groups reported in *Intensive Care Medicine* their experience of various ventilatory strategies in infants and children. First, Buettiker et al. [39] undertook a randomized clinical study of two forms of continuous positive airway pressure in 40 newborn infants. Second, Fauroux et al. [40] performed a prospective, randomized, crossover trial of three different back-up rates during pressure support and assist-control/volume-targeted ventilation in ten children with cystic fibrosis. Third, Piastra et al. [41] carried out an open study of noninvasive pressure support ventilation delivered by helmet in four children with acute leukemia. Each study yielded new and positive results.

Basic care of intubated, ventilated children includes chest physiotherapy and endotracheal tube suction. Two groups have studied these practices in a very detailed manner. First, Main et al. [42, 43] looked at the effects of respiratory physiotherapy and suction on expired tidal volume (V_{TE}), respiratory compliance (C_{rs}), respiratory resistance (R_{rs}), respiratory deadspace, and arterial blood gases. Physiotherapy appears to have an advantage in reducing R_{rs} in some patients. Within individuals, physiotherapy treatments were also more likely to produce improvements in V_{TE}, C_{rs}, and R_{rs} than suction. Argent and Morrow [44] discussed these data in an editorial, and their comments are also worth reviewing. One important question that they raised is the effect of these procedures on patient outcome. They wrote that, "Any benefit must be balanced against the costs of the procedure: costs to the patient of undergoing potentially distressing procedures of significant duration and with well-documented side effects, and costs of staff spending up to 33 minutes per patient performing the procedures." The other group in this field, Morrow et al. [45], explored some consequences of endotracheal tube suction using an in vitro "bag-in-box" model of the airway and lungs. Their results indicated that changes in intrapulmonary pressure generated by endotracheal suctioning are likely to be considerable and may possibly result in loss of lung volume.

In relation to reports concerning mechanical ventilation there were four other important studies. Arenas-Lopez et al. [46] documented their experience with an adjunctive therapy: oral clonidine for sedation in 24 ventilated children (median age 3 months). This practice is creeping into "standard care," and it is important that we see more of such pharmacokinetic data. In the laboratory Ingimarsson et al. [47] studied the effect of prophylactic surfactant supplementation in the newborn period and found that it does not protect infant lungs against the harmful effect of large lung inflations. Riou et al. [48] validated the reproducibility of measurements of respiratory dead space in mechanically ventilated children using the CO_2-SMO Plus capnograph. Markhorst et al. [49] used a mathematical model of primary (pulmonary) acute respiratory distress syndrome to examine the optimal strategy for lung recruitment. They found that none of the objective characteristics of the pressure-volume curve predicts end-expiratory atelectasis, overstretching, or optimal airway pressure.

Infection

The second major area of pediatric and neonatal research in 2004 was the study of infection and its consequences and treatments. Fidler et al. [50] studied genetic susceptibility and severity of SIRS. The authors' hypothesis was that children with mannose-binding lectin (MBL) gene polymorphisms (i.e., those associated with low levels of the functional protein) have an increased risk of developing sepsis and SIRS. In a PICU population of 100 patients, in which 50 had infections and 50 noninfectious insults as the reason for admission, *MBL-2* exon 1 polymorphisms were associated with a greatly increased risk of developing SIRS and a progression from infection to sepsis and septic shock. In the accompanying commentary, Carcillo [51] described the significance of these results and reminded us of the clinical criteria developed by Bone et al. [52] to identify critically ill patients with systemic inflammation. He concluded that the report by Fidler et al. suggests presently used definitions of SIRS/sepsis to be not only operative but also functional. The data imply that this form of critical illness, SIRS/sepsis, although a "recent" event, is associated with genetic deficiency in host ability to localize infection and inflammation.

On a similar theme—inflammation in sepsis—Pavcnik-Arnol et al. [53] studied 60 infants and children with SIRS (33 of whom had sepsis), with the aim of establishing an earlier diagnosis. The authors found that early

in the time course of illness the LPS-binding protein level is a better marker of sepsis than IL-6 and C-reactive protein. Likewise, Gulcan et al. [54] reported their experience with acridine orange, a fluorochrome stain of nucleic acids, as a diagnostic test of nosocomial pneumonia in neonates. In a series of 53 infants the test on tracheal aspirate had a positive predictive value of 100% and a negative predictive value of 83%.

Regarding infection in children, there were three other key studies in *Intensive Care Medicine*. Infection with respiratory syncytial virus (RSV) is a major cause of admission to the PICU. Eisenhut et al. [55] reported that the disease is more severe in ventilated infants with RSV infection if transaminase levels are elevated. Similarly, Tasker et al. [56] reported that there is a greater degree of lymphopenia and neuroendocrine hormone stress response in those with more severe illness. PICU patients had significantly higher prolactin and growth hormone and significantly lower leptin and insulin-like growth factor-1 levels. Taken together the data of Eisenhut et al. and Tasker et al. suggest a systemic response to infection with RSV, which clearly warrants further study. Hemodynamic support of patients with refractory shock is a problem common to pediatric and adult critical illness. Rodriguez-Nunez et al. [57] recently applied an adult therapy to pediatric patients; the authors reported their use of terlipressin in catecholamine-resistant septic shock in four children.

Organization and outcome

The third major area of pediatric and neonatal research in 2004 was the study of PICU organization and outcome. Interhospital transport and prevention of adverse events were two of the organizational topics. In regard to transport Vos et al. [58] compared interhospital pediatric intensive care transport in The Netherlands that is accompanied by a referring clinician and that undertaken by specialist retrieval teams. During transports accompanied by nontrained referring pediatricians there was a higher incidence of complications. The implication of this finding is that patient transfer should be the domain of the critical care team. The real question, however, is whether there is a practical alternative. In contrast to these findings in Europe, Goh and Abdel-Latif [59] studying the resource-limited environment of Malaysia found an alternative to specialized retrieval; the use of a pretransport checklist led to important interventions and improvements in care during transport by nonspecialists. As part of the evidence in support their argument these authors presented their "adverse event" data in a standard format. It was therefore interesting to have Tibby et al. [60] introduce us to a "systems approach" to study adverse events. Their example was the role of factors such as workload, skill mix, and staff supervision in causing adverse events. The report highlighted a systematic approach that is amenable to statistical study and can be used as a framework for strategies to reduce the occurrence of adverse events.

Two reports were devoted to outcome of pediatric intensive care. Rees et al. [61] presented novel data on the late effect of PICU admission. More features of PTSD were observed in the PICU cohort 3–12 months after admission. Furthermore, PTSD diagnosis and symptoms were more common in families in which a child had been admitted to PICU (27% vs. 3%, $p<0.05$). The clear message is that consideration should be given to providing psychological support for children and parents after PICU admission. Cooper et al. [62] reported the results of their retrospective assessment of outcome in infant and children with human immunodeficiency virus infection treated in a PICU between August 1992 and July 2002. Of the 42 children 16 (38%) died in PICU. Twenty-one patients survived to the time of reporting; 18 of these had favorable outcomes in terms of growth and development. The authors concluded that intensive care treatment in the UK is appropriate for this group of patients.

Hematology

The fourth topic, that of hematology and blood products, was covered in two key articles. Risch et al. [63] undertook a systematic review of the literature on heparin-induced thrombocytopenia in children: the clinical characteristics, therapy, and outcomes. Egan et al. [64] retrospectively evaluated their use of recombinant activated factor VII in six pediatric cardiac surgical cases with excessive and persistent bleeding.

Others

In 2004 we also presented six articles that, although not belonging to a single topic, addressed specific questions about the care of children needing intensive care. Stiller et al. [65] studied which mechanical circulatory support system for intractable heart failure causes least problems with coagulation and blood loss. Siedl et al. [66] investigated whether near-infrared photoplethysmography can be used in neonates to assess anemia and the response to transfusion. Trabold et al. [67] assessed the potential of transcranial Doppler to predict outcome in children with moderate and severe head injury. Nagdyman et al. [68] evaluated the relationship between measurements made with near-infrared spectroscopy of the brain and central venous oxygen saturation in children after corrective surgery for congenital heart disease. Pezzati et al. [69] determined the incidence of cardiac tamponade related to peripherally inserted central venous vascular catheters in newborns weighing less than 1.5 kg. Van der Kuip et al.

[70] reviewed the strategies in nutritional management in over 100 European PICUs.

Experimental studies

Despite its principal focus on clinical investigations *Intensive Care Medicine* also published a number of experimental studies on four subjects. One-half of these contributions (49%) addressed questions concerning pathophysiological pathways and/or innovative therapeutic strategies for the management of SIRS, sepsis, and septic shock. The other one-half of the published papers were distributed almost equally between studies dealing with mechanical ventilation (19%), monitoring techniques (16%), and CNS problems (11%).

Pathophysiology and treatment of sepsis

In accordance with the current interest in cell biology, a number of studies focused on apoptosis and signal transduction. In a well-established long-term bovine model of endotoxemia with or without norfenefrine-masked hypovolemia Baba et al. [71] studied heart cell apoptosis (terminal deoxynucleotidyl transferase mediated nick end labeling, TUNEL, assay) and the myocardial expression of the heat shock protein HSP72. In contrast to cellular micronecroses, both apoptosis and HSP concentration were directly related to the degree of cardiac failure as derived from the prefinal catecholamine doses as well as parameters of systolic function (left ventricular stroke work index). Le Berre et al. [72] investigated whether inhibition of apoptosis as determined using the using the caspase inhibitor Z-VAD-fluoromethylketone would affect lung fluid balance in a rat model of *Pseudomonas aeruginosa* induced pneumonia. Reduction in apoptosis-related DNA fragmentation as determined using the TUNEL assay and the measurement of caspase-3 activation improved pulmonary fluid balance as derived from endothelial permeability and lung wet-to-dry weight ratio. Other studies investigated the role of signal transduction, for example, that of nuclear factor (NF) κB activation in models of inflammation, endotoxemia, and sepsis. In endotoxin-challenged rats Lim et al. [73] found that deliberate hypothermia (37° vs. 27°C body temperature) markedly reduces pulmonary inflammation, and Virlos et al. [74] demonstrated that calpacain I inhibitor attenuates cerulein-induced pancreatitis in mice. In both models NF-κB activation was inhibited, which coincided with a decreased release of both inflammatory cytokines and peroxynitrite and reduced the expression of both the inducible isoform of the nitric oxide synthase (iNOS) and the poly-(ADP-ribose)-polymerase (PARP). Similar findings on peroxynitrite formation were reported by Cuzzocrea et al. [75] in a model of murine acute pancreatitis when animals were pretreated with the peroxisome proliferator-activated receptor γ agonist rosiglitazone. This group of investigators also studied other pathophysiological pathways. In a murine model of multiple organ failure resulting from zymosan-induced nonseptic peritonitis the authors showed that 5-lipoxygenase k.o. strains had less pronounced inflammatory response, ultimately leading to improved survival [76], and in rats challenged with intraperitoneal zymosan exposure to hyperbaric oxygen (HBO), for example, pure oxygen breathing at supra-atmospheric ambient pressures (2 bar), blunts the cardiovascular derangements [77]. This beneficial effect of HBO was associated with reduced iNOS activation and peroxynitrite formation and, strikingly, attenuated oxidative stress to the tissues. The latter study was accompanied by an editorial comment by Bitterman and Muth [78]. Another "old" therapy, intraperitoneal injection of high-doses of the well-known mucolytic ambroxol, was studied in mice with acute lung injury (ALI) induced by intratracheal instillation of endotoxin. Ambroxol was compared with dexamethasone administration. Both compounds reduced pulmonary inflammation and accelerated the recovery from ALI.

Despite the existing plethora of experimental studies dealing with iNOS and/or PARP activation in various shock models a number of additional aspects were addressed this year in *Intensive Care Medicine*. In rats with acute lung injury resulting from bleomycin-inhalation Jang et al. [79] demonstrated developed chronic (4–14 days) overexpression of both iNOS and constitutive endothelial isoform (eNOS) while the neuronal isoform remained unchanged. These results also underscore the crucial role of the type of injury and the timing of the investigation, since in contrast to these findings Fischer et al. [80] reported in rats with cecal ligation and puncture induced peritonitis that only pulmonary iNOS expression was increased at 24 h of sepsis while eNOS was even reduced. The authors further demonstrated that nonselective NOS inhibition with N^{ω}-nitro-L-arginine methylester increases the degree of hypoxic pulmonary vasoconstriction in these animals whereas, interestingly, selective iNOS blockade with L- N^6-(1-iminoethyl)-lysine had no effect. Two other studies focused on the role of iNOS and PARP, i.e., on the interplay of increased production of reactive oxygen species, the concomitant formation of peroxynitrite from superoxide and NO, and the subsequent activation of PARP. In cecal ligation and puncture challenged rats, Nin et al. [81] found that both the NOS inhibitor aminoguanidine and the novel antioxidant Mn-pyridinium-porphyrin ameliorate the sepsis-related diaphragmatic dysfunction and ultimately organ failure, which was affiliated with improved mitochondrial respiration. In addition, inhibition of PARP using 3-aminobenzamide in endotoxin-challenged rabbits attenuated iNOS mRNA expression as a result of reduced activation of activator protein 1 (and, interestingly, without

effect on NF-κB), which was accompanied by a marked reduction in tissue reactive oxygen species production and cellular injury and in improved pulmonary gas exchange. Finally, Asfar et al. [82] addressed the question whether inhibition of the ATP-dependent K^+ channels, a pathophysiological pathway downstream of the NO activation, which is considered a mediator of both vascular and cellular energy failure, could be of therapeutic value for the management of patients with sepsis. Using a post-treatment approach in a well-established long-term porcine model of hyperdynamic endotoxemia the authors infused the newly developed KATP channel blocker HMR1403. The transitory hemodynamic stabilization was outweighed by the marked aggravation of the endotoxin-related disturbance of the cytosolic redox potential.

In line with the current interest in altered capillary perfusion in the context of sepsis-related organ dysfunction several papers dealt with potential therapeutic interventions targeted to improve (micro)vascular function. Anning et al. [83] demonstrated that the clinical day-to-day measure of *early* aggressive fluid resuscitation leads to present LPS-induced mesenteric microvascular permeability as well as leukocyte rolling and adhesion as assessed using intravital microscopy in rats. Interestingly, this effect was unrelated to the total microvascular flow, and no difference was observed whether saline or albumin was used as resuscitation fluid. Other therapeutic options aiming at improving microvascular perfusion and endothelial function were investigated by Lehmann et al. [84], Wiel et al. [85], and Adolphs et al. [86] in endotoxin-challenged rodents. With a similar intravital microscopy approach in rats to that used by Anning et al., Lehmann et al. [84] demonstrated that C1 esterase inhibitor increases intestinal functional capillary density and reduces leukocyte adherence and plasma extravasation. Also in rats Adolphs et al. [87] showed that epidural anesthesia-induced sympathicolysis not only causes heart rate and blood pressure to fall, presumably as a mirror of decreased cardiac output, but also reduces mucosal perfusion while the blood flow to the muscularis layer is not affected. This contribution was accompanied by an editorial comment by Sielenkämper and Van Aken [88]. Finally, Wiel et al. [85] found that inhibiting angiotensin-converting enzyme in rabbits prevents endotoxin-related disturbance of mesenteric endothelial functional and morphological injury. The latter finding was clearly related to an NO-dependent mechanism.

Mechanical ventilation

Mechanical ventilation is undoubtedly one of the cornerstones of intensive care medicine, and thus a number of articles addressed both pathophysiological and technical aspects of artificial respiratory support. Four papers focused on the inflammatory response affiliated with various ventilatory modes. Schortgen et al. [89] studied rats 1 day after right lung instillation of *P. aeruginosa*, i.e., induction of unilateral pneumonia. During left lateral positioning different levels of PEEP (0 vs. 8 cmH_2O) with low tidal volume ventilation (V_T 6 ml/kg) were compared with high V_T/0 PEEP ventilation and partial liquid ventilation (PLV) at PEEP 3 cmH_2O. While only low V_T/8 cmH_2O ventilation prevented contralateral bacterial dissemination, PEEP per se attenuated the systemic inflammatory responses as assessed by blood TNF-α. Broccard [90] accompanied this contribution with an editorial comment. The impact of mechanical ventilation on the bacterial burden was further studied in rabbits by Charles et al. [91], who compared spontaneous respiration with mechanical ventilation at 0, 5, and 10 cmH_2O PEEP with respect to lung bacteria count, lung weight, and histology after inoculation of *Enterobacter aerogenes* to induce pneumonia. When compared to spontaneous breathing, mechanical ventilation per se led to aggravation of lung injury, and, interestingly, 0 and 10 cmH_2O had similar effects, while ventilation at lower PEEP levels induced less injury. Another aspect of PLV application, i.e., the time dependence of its therapeutic potential, was studied in rabbits after intratracheal instillation of hydrochloric acid by Pakulla et al. [92], who demonstrated that early (5 vs. 30 min after acid instillation) PLV application reduces pulmonary neutrophil accumulation and ultimately improved survival. Finally, Krishnan et al. [93] compared two types of lung recruitment strategies, i.e., high-frequency oscillation and conventional volume-targeted mechanical ventilation, in newborn piglets that had undergone surfactant washout. Neither lung mechanics, release of proinflammatory cytokines, nor morphometric and histopathological data showed any major differences. Using a similar lavage-induced porcine model of acute lung injury Henzler et al. [94] tested the hypothesis of whether improved ventilation-perfusion (V_A/Q) matching during biphasic positive airway pressure (BiPAP) with preserved spontaneous breathing is caused by an effective increase in transpulmonary pressure and can thus also be achieved during pressure-controlled ventilation. BiPAP was compared to conditions of similar transpulmonary and airway pressures. V_A/Q distributions were similar in the three experimental groups, but BiPAP with preserved spontaneous respiration caused less cardiovascular compromise. This contribution was accompanied by an editorial comment by Calzia and Bein [95].

Finally, lavage-induced ALI in swine was used to test new technical modifications for optimizing conventional mechanical ventilation. Lethvall et al. [96] evaluated a double-lumen endotrachael tube designed to reduce dead space ventilation. Compared to a standard endotracheal tube this device markedly reduced arterial PCO_2 at low tidal volume ventilation without any change in airway pressure or the occurrence of an auto-PEEP phenomenon. Lindgren et al. [97] from the same group compared closed

and open suctioning during pressure-controlled ventilation (PCV) and continuous positive airway pressure (CPAP) breathing. While both modes of suctioning markedly depressed blood oxygenation, this effect was considerably attenuated with closed suctioning during PCV.

Monitoring

Close monitoring of physiological variables is a further characteristic feature of intensive care medicine, and the assessment of hemodynamics, lung function, and metabolic status were therefore also addressed in experimental studies. Given the current discussion on the determination of optimal cardiac preload and volume responsiveness, two contributions addressed the effect of variations in airway pressure on systemic hemodynamics. In ventilated sheep, Luecke et al. [98] studied the effect of increasing incremental PEEP (0, 7, 14, and 21 cmH_2O) on left ventricular enddiastolic volume to determine whether right ventricular enddiastolic volume (RVEDV) or intrathoracic blood volume (ITBV) is superior to filling pressures as markers of cardiac preload. While incremental PEEP did not alter right ventricular function, it impaired the left heart, and both RVEDV and ITBV provided reliable estimates of left ventricular preload even at high intrathoracic pressures. In contrast to the direct assessment of volumetric parameters, Slama et al. [99] demonstrated in mechanically ventilated rabbits that respiration-induced variations in aortic blood flow velocity measured using an esophageal Doppler device precisely predicted both the degree of volume depletion due to blood withdrawal as well as the efficiency of a subsequent restitution.

New possibilities for determinating lung mechanics were studied by two other groups. Bitzen et al. [100] analyzed the relationship between inspiratory and expiratory static and dynamic pressure-volume curves in the lungs of healthy, anesthetized, and ventilated swines. Using a computer-controlled ventilator to achieve a sinusoidal modulation of inspiration and expiration from 0 to a maximum of 50 cmH_2O PEEP, the authors showed that viscoelastic properties of the lung affect the pressure-volume relationships, and that both lung collapse and reexpansion are indicated by hysteresis. To determine functional residual capacity, Schibler et al. [101] compared three different N_2 and SF_6 washout techniques as derived from the mass signal of an ultrasonic flow meter in monkeys either breathing spontaneously or during mechanical ventilation. The authors found that both techniques compared well with the "gold standard" mass spectrometry and thus provide simple and reliable alternatives for this purpose. Finally, two other studies dealt with metabolic problems. Solligard et al. [102] showed in anesthetized and ventilated swine undergoing 60 min of thoracic aortic cross clamping and subsequently 2 h of reperfusion that intestinal luminal microdialysis of glycerol and lactate agree well with the ischemia reperfusion-related gut wall injury, documented by the increased intestinal permeability. In ventilated rats, Morgan et al. [103] showed that normovolemic hemodilution using several different electrolyte solutions may cause metabolic acidosis, and that the degree of this metabolic acidosis is directly related to the strong ion content of the infused solution.

CNS problems

The pathophysiology and therapeutic management of brain disorders has gained increasing interest in intensive care research in recent years, and this development is also reflected in experimental studies of this journal. The effects of hyperventilation ($PaCO_2$ approx. 25 mmHg) together with hyperoxia (FIO_2 1.0) on cerebral hemodynamics (intracranial and cerebral perfusion pressure) and metabolism (tissue blood gases, pH, glucose, and lactate levels) as assessed using tissue gas sensors and microdialysis were compared with normoventilation in swine 2 h after induction of cerebral arterial gas embolism [104]. None of these parameters was improved by this therapeutic strategy. This contribution was accompanied by an editorial comment by Muth and Shank [105]. Burkhardt et al. [106] investigated whether increasing FIO_2 from 0.5 to 1.0, either during conventional mechanical ventilation or during PLV with two different liquid volumes applied would affect cerebral oxygen supply in healthy, anesthetized piglets. Initiation of PLV caused cerebral oxygenation to fall, and well-maintained cerebral oxygen supply was possible only using small liquid volumes together with pure O_2 breathing. Kocaogullar et al. [107] studied anesthetized rats to test whether exposure to hyperbaric oxygen (HBO, 60 min at 3 bar) would improve neurological function after subarachnoid hemorrhage. The authors demonstrated that animals with cerebral vasospasm after inoculation of homologous blood into the cisterna magna recovered more quickly after HBO treatment than after normobaric hyperoxia, i.e., pure O_2 at atmospheric pressures. Finally, in anesthetized and ventilated rats Trübel et al. [108] investigated a new technique allowing selective brain cooling (to approx. 33°C) at virtually normothermic whole-body conditions via a heat exchanger placed into the pharynx. The authors demonstrated the feasibility of this approach and furthermore showed that both induction of seizure activity and a hypercapnic challenge ($PaCO_2$ approx. 80 mmHg) increase brain temperature, probably as a result of the concomitant rise in cerebral blood flow.

Miscellanous

Additional studies dealt with other common problems of intensive care medicine. Frühwald et al. [109] used their well-established in vitro model of isolated guinea pig small bowel segments to study the effects of various drugs commonly used in intensive care practice on gut motility as assessed by measuring the peristaltic pressure threshold. Cerulein stimulated peristalsis at all concentrations tested, while neostigmine had prokinetic properties only at low tissue levels. The higher neostigmine concentrations, however, were necessary to reverse the inhibitory effects of epinephrine and sulfentanil. Asakura et al. [110] investigated the impact in rats of pretreatment with low molecular heparin on the degree of endotoxin-related disseminated intravascular coagulation. While this attenuated the severity of the condition and both kidney and liver injury, additional suppression of fibrinolysis with tranexamic acid actually increased organ damage. Haas et al. [111] studied anesthetized and ventilated pigs with massive pulmonary embolism induced by stepwise microsphere injection to evaluate the therapeutic potential of incremental Mg^{2+} under these conditions. In a dose-dependent manner Mg^{2+} improved pulmonary hemodynamics, and there were no major deleterious effects on systemic hemodynamics at the lower Mg^{2+} doses used. At these doses Mg^{2+} plasma concentrations were close to values under conditions found during administration Mg^{2+} for other purposes. Finally, Sen et al. [112] tested the hypothesis that albumin dialysis using a molecular adsorbents recirculating system would improve drug removal after intoxication with protein-bound compounds. In pigs with experimental liver failure this approach effectively reduced the total and free plasma concentrations of midazolam and fentanyl, together with a marked decrease in the albumin content.

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