Review

Year in review 2006: *Critical Care* – multiple organ failure, sepsis, and shock

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Abstract

In 2006, *Critical Care* provided important and clinically relevant research data in the field of multiple organ failure, sepsis, and shock. This review summarizes the results of the experimental studies and clinical trials and discusses them in the context of the relevant scientific and clinical background.

Introduction

Sixteen papers focusing on sepsis and multiorgan failure were published in *Critical Care* in 2006. Five of them focused on microcirculation studies in sepsis, thereby concentrating on endothelial and leukocyte activation. Another two papers focused on the effects of hypothermia in sepsis and surgery, on mitochondrial and organ function during sepsis, and on lung injury. Finally, five papers, including one presenting a meta-analysis, were based on clinical trials.

Microcirculation, leukocyte adherence, and endothelial activation during sepsis

Microvascular blood flow abnormalities are recognized as one of the key features of experimental and human sepsis. They are reported to contribute to organ dysfunction and poorer outcome in sepsis [1,2]. In this context, intestinal microcirculation is of great interest because the hepatosplanchnic region is believed to assume a crucial role for both the initiation and aggravation of sepsis [3]. Birnbaum and colleagues [4] compared the effects of simultaneously administering the coagulation factor XIII and endotoxin (2.5 mg/kg per hour lipopolysaccharide [LPS] for 2 hours) to endotoxin or saline administration alone. Intestinal functional capillary density (FCD), leukocyte adherence in the intestinal microcirculation, and mesenteric plasma extravasation were evaluated in rats by means of intravital microscopy (IVM). Both endotoxemic groups showed increased leukocyte adherence and reduced intestinal mucosal FCD. However, there were no changes either in the FCD of intestinal circular and longitudinal muscle layers or in mesenteric plasma extravasation after endotoxin. Factor XIII administration attenuated the reduction of mucosal FCD only, whereas it failed to affect any of the other parameters examined. In a similar model, the same group investigated intestinal microvascular blood flow and leukocyte adherence in rats treated with dopexamine after the endotoxin challenge [5]. In contrast to the previous setting, endotoxemia was performed with 20 mg/kg LPS for a period of 15 minutes. Interestingly, endotoxemia did not induce any changes in intestinal mucosal FCD but decreased FCD in circular and longitudinal muscle layers of the small intestine. Treatment with dopexamine both attenuated the endotoxin-induced decrease in intestinal microvascular blood flow estimated using laser Doppler flowmetry and reduced the number of firmly adherent leukocytes in intestinal submucosal venules. IVM also showed an enhancement of FCD in intestinal muscle layers in the dopexamine-treated group.

Another study of the intestinal microvasculation during endotoxemia tried to shed light on the already recognized beneficial effects of activated protein C (APC) in the treatment of sepsis [6]. In animal models of sepsis, APC was associated with improved organ function [7,8], and several

ADMA = asymmetrical dimethyl arginine; ALI = acute lung injury; AP-1 = activating protein-1; APC = activated protein C; AR = adenosine receptor; ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; COX-2 = cyklooxygenase-2; CPB = cardiopulmonary bypass; DDAH = dimethylaminohydrolase; DHEA = dehydroepiandrosterone; DrotAA = drotrecogin alfa (activated); ERK = extracellular signal-regulated kinase; FCD = functional capillary density; HUVEC = human umbilical vein endothelial cell; IL = interleukin; iNOS = inducible nitric oxide synthase; I/R = ischemia/reperfusion; IVM = intravital microscopy; JNK = c-Jun amino-terminal protein kinase; LPS = lipopolysaccharide; MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor kappa B; NO = nitric oxide; NOS = nitric oxide synthase; SOFA = sequential organ failure assessment; TAC = total antioxidant capacity; TNF-α = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor.

different mechanisms may be responsible for these findings. Using IVM, Lehmann and colleagues [9] estimated FCD in mucosal and circular and longitudinal muscle layers as well as the leukocyte adherence in intestinal submucosal venules after a single bolus of 15 mg/kg LPS alone or followed by subsequent injection of human recombinant APC. Plasma levels of inflammatory mediators tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-10 were measured also. The endotoxic animals showed both decreased FCD in the mucosal and circular and longitudinal muscle layers of the terminal ileum and increased leukocyte adherence in submucosal venules. APC attenuated these effects but failed to decrease plasma levels of inflammatory cytokines. No differences that could be attributed to APC treatment were observed between the two control groups, in which either saline or APC alone was given.

A very interesting study was presented by Croner and colleagues [10], who tried to elucidate the time course and reciprocal influences of microperfusion, platelet adherence, and leukocyte–endothelial interactions in the hepatic microcirculation during sepsis in rats. Immediately after cecal ligation and puncture, the IVM of liver was started. Unfortunately, no control group was included in this study, so the contribution of anesthesia, missing volume resuscitation resulting in hypovolemia, and any putative reaction to the administration of labelled erythrocytes and thrombocytes from donor rats could not be evaluated.

Experimental studies suggest that sex hormones assume importance for both the post-traumatic immune response and cardiac function [11,12]. Dehydroepiandrosterone (DHEA), the precursor of androstendione, testosterone, and estrogen, is synthetized in gonads and adrenal glands of both males and females, whereas the synthesis in the adrenal gland becomes of increasing importance in elderly men and women. The conversion to sex hormones depends on sex-steroid-converting enzymes in gonads and peripheral tissues (for example, adipose tissue, muscles, skin, and lymphatic tissue). Several animal models showed a beneficial effect of DHEA administration in male mice after experimental trauma-hemorrhage and/or sepsis, thereby preventing immunodepression and improving outcome [13,14]. Since sepsis-related organ dysfunction is reported to be associated with the extravasation of leukocytes, Barkhausen and colleagues [15] investigated the expression of endothelial and neutrophil adhesion molecules *in vitro* after LPS stimulation and/or treatment with DHEA. In this study, cultures of human umbilical vein endothelial cells (HUVECs) and neutrophils freshly isolated from blood of male healthy volunteers were used. Expression of the adhesion molecules VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and E-selectin on HUVECs and expression of L-selectin, CD-11b, and CD-18 on neutrophiles were estimated after stimulation with LPS, treatment with both near-physiologic and pharmacological doses of DHEA (10^{-8} and 10^{-5} M, respectively), or the combination of LPS stimulation and DHEA treatment (both concentrations). DHEA modulated the adhesion molecule expression in endothelial cells and neutrophiles, and most effects were detectable within the physiological concentration. However, DHEA did not influence the adhesion molecule expression pattern after LPS stimulus. It must be noted in this context that humans produce DHEA in much greater quantities than any other species. Even non-human primates present with only 10% of the relative serum level of DHEA observed in humans. The fact that rodents produce so little DHEA renders such experimental results controversial. In fact, in a porcine model of hemorrhagic shock, DHEA administration did not have any significant beneficial effect [16]. It must be taken into account, however, that the lacking beneficial effect might also be ascribed to the immaturity of the animals, since adolescent pigs were used in this experiment.

Lung injury

Acute lung injury (ALI), along with its most severe form, acute respiratory distress syndrome (ARDS), is one of the most challenging conditions in critical care medicine. The focus has been the role of vascular endothelial growth factor (VEGF), which is reported both to considerably increase microvascular permeability and to induce proliferation and anti-apoptotic signaling in both vascular endothelial and alveolar epithelial cells [17-19]. These effects might assume major importance in ALI/ARDS, promoting lung edema on the one hand, but protecting lung epithelial cells and inducing cell recovery on the other hand. Mura and colleagues [20] estimated the VEGF expression in lung tissue and its concentration in plasma and the bronchoalveolar lavage (BAL) fluid in an extrapulmonary model of ALI induced by intestinal ischemia/reperfusion (I/R) in rats [20]. Decreased VEGF expression in lung tissue and diffuse increase of interstitial cellularity, interstitial edema, and vascular congestion together with enhanced severity of lung injury were observed in the intestinal I/R group. These findings are consistent with most observational studies of lung injury in humans, showing reduction in intrapulmonary VEGF levels in the early stages of ARDS. Whereas there were no intergroup differences in VEGF plasma levels, protein concentration, total cell count, and percentage of neutrophils were increased in the BAL fluid of both intestinal I/R and sham-operated animals, suggesting that mechanical ventilation and/or hyperoxia may be responsible for these findings. VEGF concentration in the BAL fluid was higher in both ventilated groups compared to mice breathing air spontaneously (control group), probably simply reflecting the increased protein leakage, as the lung permeability assessed by Evans blue dye permeability assay did not differ between control and sham-operated groups. In the long term, treatment modulating VEGF may be of value in ARDS, but the challenge will be to limit the effects of such treatment to those desired, given the pleotropic functions of VEGF in the body [21].

I/R-induced lung injury, which may follow situations such as lung transplantation or cardiopulmonary bypass (CPB), represents another challenging circumstance in intensive care medicine. Interestingly, selective activation of A_3 adenosine receptor (AR) subtype attenuated I/R-induced lung injury and associated apoptosis [22]. ARs couple among other types of messenger molecules to mitogen-activated protein kinases (MAPKs), which participate in anti-inflammatory/inflammatory cell signaling [23]. Three major MAPK families have been identified: the extracellular signal-regulated kinases (ERKs), the c-Jun amino-terminal protein kinases (JNKs), and p38 kinases. Notably, whereas ERK1 and ERK2 exert a cytoprotective effect and are involved in cell proliferation, transformation, and differentiation, p38 and JNK promote cell injury and apoptosis [24]. Matot and colleagues [25] evaluated MAPK activation in the reperfused lung, comparing the effects of the highly selective A_3AR agonist MRS3558 with that of the moderately selective agonist IB-MECA on lung injury and apoptosis and determined the modulation of MAPK (ERK1, ERK2, p38, and JNK) pathways after A_3AR activation in a feline model of lung I/R. Both A_3AR agonist MRS3558 and IB-MECA attenuated alveolar injury, lung edema, and inflammation and significantly decreased apoptosis. The selective agonist MRS3558 allowed the same effect with a lower dose, whereas neither MRS355M nor IB-MECA resulted in the complete restoration observed in the non-ischemic group. I/R increased the expression of all three MAPKs, with significantly greater expression of JNK and p38. Treatment with A_3AR agonist before reperfusion markedly increased ERK1 and ERK2 expression and attenuated reperfusion lung injury and apoptosis, thus presenting a promising approach for moderating lung injury and supporting recovery after clinical I/R.

Organ (dys)function in sepsis

Organ dysfunction is a hallmark of severe sepsis, and mitochondrial dysfunction is reported to be one of the key mechanisms involved. Indeed, serum from patients with septic shock significantly depressed mitochondrial respiration in endothelial cells and decreased cellular ATP levels [26]. Furthermore, in muscle biopsies from septic patients, the severity of shock, organ failure, and outcome were directly related to the decreased activity of the mitochondrial complex I, decreased ATP levels, and nitrosative and oxidative stress [27]. Finally, despite the maintenance of tissue oxygen availability, mitochondrial function was found to be significantly impaired in a feline model of acute endotoxemia, and this impairment was strongly associated with the extent of mitochondrial ultrastructural abnormalities present in the tissue [28]. Porta and colleagues [29] evaluated liver, kidney, and skeletal muscle mitochondrial function in a porcine model of prolonged resuscitated endotoxemia. Despite well-preserved hepatic oxygen extraction and consumption and even increased total hepatic blood flow, mitochondrial respiratory efficiency was decreased for both hepatic complex I and II. The mitochondrial oxygen consumption was increased in order to maintain the membrane potential, probably as a mirror of partial uncoupling of electron influx and ATP production. The hepatic venous lactate/pyruvate ratio did not change significantly until the end of the experiment. In kidney and skeletal muscle mitochondria, no significant changes in mitochondrial oxygen consumption and ATP production were seen despite significantly impaired renal blood perfusion at the end of the experiment. The findings of this study add to the above-mentioned human data and, in addition, suggest that the mitochondrial dysfunction observed is not only time-dependent [30] but also organ-specific and related to the type of shock present. Nevertheless, they provide additional support to the concept of mitochondria-targeted therapies [31].

Myocardial depression, as evidenced by biventricular dilatation and reduced ejection fraction, is reported to be present in most patients with sepsis and septic shock [32]. Although sepsis predominantly affects older persons, only few experimental data on septic organ dysfunction in the aged animal are available. Rozenberg and colleagues [33] determined the degree of dysfunction of isolated and perfused hearts from young and old rats (3 months and 24 months, respectively) subjected *in vivo* to experimental endotoxemia. Strikingly, the LPS dose had to be decreased 10 times for aged rats when "mild endotoxemia" (mortality lower than 10%) was the objective. Under basal conditions, the hearts from senescent rats showed altered left ventricular function, as demonstrated by reduced LVDP (left ventricular developed pressure) and lower peaks of the positive and negative pressure derivatives (dP/dt max and -dP/dt max). Despite the 10-fold lower LPS dose, the relative myocardial depression was similar in the two groups, resulting in a further impairment of already diminished heart function of aged rats. Interestingly, the endotoxemia-induced decrease of myofilament Ca^{2+} responsiveness was not seen in senescent hearts. This finding could be of clinical relevance if confirmed *in vivo*, as Ca^{2+} sensitizing agents may thus not be as effective in aged patients as in younger patients.

Hypothermia

Hypothermia is routinely used during cardiac surgery as it was shown to protect organs against ischemia. Qing and colleagues [34] tried to identify the cellular mechanisms associated with hypothermia-mediated myocardial protection in a porcine model of myocardial I/R injury. Standardized CPB was performed for 2 hours either at normothermic conditions (37°C) or during moderate hypothermia (28°C), in which 1 hour of aortic cross-clamping was anticipated by 30 minutes of cooling of animals and consequently was followed by 30 minutes of rewarming. Additional cooling of hearts was performed in both groups during CPB. Myocardial levels of TNF-α, inducible nitric oxide synthase (iNOS), and cyklooxygenase-2 (COX-2) as well as activation of the transcription factors c-Jun, nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), and MAPK p38 were measured

before the start of CPB, before aortic cross-clamping, before removal of the aortic clamp, and 6 hours after CPB. Systemic hypothermia attenuated activation of transcriptor factor c-Jun, MAPK p38, and its downstream effector AP-1. TNF-α expression in myocardial tissue was significantly lower in the hypothermic group 6 hours after CPB. Myocardial COX-2 levels were significantly lower in the hypothermic animals 30 minutes after the start of CPB, but neither NF-κB activation nor iNOS activation was prevented by hypothermia. This study brought new insight into mechanisms involved in hypothermia-associated attenuation of myocardial inflammation and damage after an ischemic event.

In association with sepsis, both adverse and beneficial effects of hypothermia are reported [35,36]. During hypothermia, activation of platelets is induced, possibly resulting in thromboembolic events and coagulation defects [37]. Lindenblatt and colleagues [38] evaluated the contribution of hypothermia to activation of coagulation in endotoxic mice. Systemic hypothermia (34°C and 31°C) further enhanced the endotoxin-induced acceleration of microvascular thrombus formation, in particular in arterioles, but with a significant enhancement at 31°C only. In contrast, neither endothelial cells nor platelets showed any additional activation due to hypothermia. Both the plasma levels of PAI (plasminogen activator inhibitor) and its endothelial expression were further pronounced in hypothermic groups, thus offering a possible explanation for a hypothermia-associated increase in prothrombotic disposition.

Clinical trials

Understanding the role of apoptotic cell death in sepsis and shock, especially its contribution to immune and organ dysfunction, has been studied by many laboratories in recent years. Giamarellos-Bourboulis and colleagues [39] focused on the existence of apoptosis of blood monocytes in sepsis and its correlation to the final outcome, as the triggering of the cells plays a central role in the initiation of the septic cascade. Patients with concomitant ventilator-associated pneumonia and sepsis, severe sepsis, or septic shock were included in the study. The apoptosis of isolated blood monocytes was measured on days 1, 3, 5, and 7 after both diagnoses had been simultaneously confirmed. Patients with septic shock and blood monocyte apoptosis of less than 50% at day 1 showed higher plasma levels of proinflammatory cytokines TNF-α, IL-6, and IL-8 as well as an ultimately decreased 28-day survival. Accordingly, the comparison between 28-day survivors and non-survivors of septic shock showed higher blood monocyte apoptosis in survivors at days 1 and 5. Interestingly, there was no difference in the rate of apoptosis at days 3 and 7. The authors suggest that apoptosis of blood monocytes could be a beneficial mechanism during septic shock, protecting the organism against overwhelming inflammatory response due to a decreased release of proinflammatory cytokines. Another aspect to consider is that a higher rate of blood monocyte apoptosis may mirror a better balanced regulation of the inflammatory response *per se.*

Oxidative stress is commonly present in inflammatory diseases. 'Total antioxidant capacity' (TAC) describes the ability of a biological sample (serum or plasma, tissue extract) to inhibit the transformation of a selected substrate by an *in vitro*-generated free radical [40]. Depending on the method used, the plasma or serum TAC usually involves major contributions from urate, ascorbate, and sometimes albumin sulfhydryl groups [41]. Chuang and colleagues [42] compared serum TAC of patients with severe sepsis with that of healthy individuals matched to the patients with respect to age and gender. The serum TAC level of patients with sepsis was significantly higher than that of the healthy controls. Furthermore, the severity of sepsis evaluated by APACHE II (Acute Physiology and Chronic Health Evaluation II) score was directly related to the serum TAC levels. A strong correlation between TAC and uric acid levels in patients with severe sepsis confirmed the contribution of urate to TAC estimation. Bilirubin, but not albumin, contributed to serum TAC level in this study as well. Because plasma levels of these molecules change due to altered organ functions, other methods should be used to evaluate oxidative stress in the critically ill [40].

Asymmetrical dimethyl arginine (ADMA), a non-selective inhibitor of nitric oxide synthase (NOS), is a byproduct of protein (amino acid) metabolism. Its amount is regulated by the scavenging enzyme dimethylaminohydrolase (DDAH), of which two isoforms (I and II) are known. DDAH II has an expression pattern similar to that of endothelial NOS [43]. In cardiovascular diseases such as atherosclerosis, the amount of endothelial dysfunction and nitric oxide (NO) bioavailability correlated well with increased plasma levels of ADMA [44]. In sepsis, excessive NO formation causes vasodilatation but also assumes crucial importance in antimicrobial host defense. Experimental inhibition of NO synthesis during sepsis showed controversial results [45]. O'Dwyer and colleagues [46] estimated the serum plasma level of ADMA and IL-6 on days 1 and 7 after intensive care unit admission in patients with severe sepsis and septic shock and evaluated its association with vasopressor requirement. Plasma ADMA levels correlated with both lactate levels and the sequential organ failure assessment (SOFA) score, even if the cardiovascular component was excluded from the total SOFA score. On day 7, IL-6 level correlated with ADMA level also. The patients requiring vasoactive drugs had higher levels of ADMA, higher SOFA score, and increased mortality. At first glance, this finding is striking since ADMA, the endogenous inhibitor of NOS, would be expected to induce vasoconstriction. On the other hand, one might speculate that increased ADMA levels might reflect an adaptive response against excessive NO production. The promoter region of the *DDAH II* gene exists as C and G allelic variants. Carriage of the G allele was associated with increased

ADMA production of both day 1 and day 7. Only 11% of septic patients were CC homozygotes; however, further investigation is needed to establish whether this polymorphism may be used as a marker for the susceptibility to and severity of an inflammatory response secondary to an infectious insult.

A proper function of hypothalamic-pituitary adrenal axis is mandatory for an adequate stress response and for the maintenance of homeostasis in stress situations. Numerous factors, including various drugs, interfere with the hypothalamic-pituitary axis [47]. Classical clinical and laboratory findings of acute adrenal insufficiency (hypotension, hypoglycemia, fever, abdominal pain, or electrolyte abnormalities) cannot be distinguished from those of sepsis. That is why adrenal function tests are needed to identify patients with sepsis who may profit from glucocorticoid therapy. Although the diagnostic criteria for adrenal failure in a non-acutely ill population are well established, there is no consensus for the critically ill. Salgado and colleagues [48] measured baseline total cortisol as well as cortisol levels after sequential 1 μg and 249 μg corticotropin administration (cortisol 60 and cortisol 120, 60 minutes after each test) and calculated Δmax^{1} and Δmax^{249} (cortisol 60 – baseline cortisol and cortisol 120 – baseline cortisol) values. Clinical adrenal failure was defined as removal of norepinephrine up to 120 hours after hydrocortisone treatment. Hydrocortisone (100 mg intravenously three times per day) therapy was not administered according to a predefined protocol but at the discretion of the attending physician. Neither the baseline cortisol value nor Δmax^{1} and Δmax^{249} values were able to predict the norepinephrine removal in the general population or in the hydrocortisone-treated group. In hypoalbuminemic patients, significantly lower baseline cortisol and cortisol at 60 and 120 minutes were found, suggesting the potential of overestimation of adrenal failure in the presence of hypoalbuminemia. As no association between serum albumin level and Δmax^{1} and Δmax^{249} was found, these calculations offer an alternative to free cortisol estimation and may prevent the false-positive diagnosis of adrenal failure influenced by low serum albumin [49].

Drotrecogin alfa (activated) (DrotAA), also known as human recombinant APC, was shown to improve outcome after sepsis, but unsuccessful clinical trials of DrotAA treatment of less severe patients and children have questioned the unequivocal efficacy of this drug [50]. Data of patients receiving either DrotAA or placebo enrolled in five trials of severe sepsis with similar entry criteria and conducted by a single sponsor were used to construct an integrated database named INDEPTH (International Integrated Database for the Evaluation of Severe Sepsis and Drotrecogin alfa [activated] Therapy) [51]. Vincent and colleagues [52] used this database to evaluate the effect of timing of DrotAA treatment in severe sepsis. Kaplan-Meier 28-day survival curves showed significantly higher 28-day survival for patients treated with DrotAA earlier (0 to 24 hours) than for patients treated later (more than 24 hours, 76.4% and 73.5%, respectively). Both DrotAA time-to-treatment curves were significantly different from the placebo time-to-treatment groups. No timing-related differences were observed in the placebo 28-day survival curves (0 to 24 hours, 68.1%; more than 24 hours, 67.8%). This finding does not support the indication that solely early identification as well as treatment of patients with severe sepsis with standard supportive care is responsible for improved outcome after early treatment with DrotAA [53]. However, it does suggest that early identification and treatment of patients with severe sepsis and consequently early treatment with DrotAA may provide the highest benefit for these patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VS, KB, and EB contributed equally to the drafting of the manuscript. PR and EC revised it critically for important intellectual content. PR has given final approval of the version to be published.

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