Review
Year in review 2007: *Critical Care* – shock

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Abstract

The research papers on shock published in *Critical Care* throughout 2007 are related to three major subjects: the modulation of the macrocirculation and microcirculation during shock, focusing on arginine vasopressin, erythropoietin and nitric oxide; studies on metabolic homeostasis (acid–base status, energy expenditure and gastrointestinal motility); and basic supportive measures in critical illness (fluid resuscitation and sedation, and body-temperature management). The present review summarizes the key results of these studies and provides a brief discussion in the context of the relevant scientific and clinical background.

Introduction

Nine original articles focusing on shock were published in *Critical Care* during 2007. Four papers concentrated on the effects of innovative therapeutic strategies on the macrocirculation and microcirculation in animal models of sepsis or hemorrhage, thereby focusing on arginine vasopressin (AVP), erythropoietin (EPO) and inducible nitric oxide synthase (iNOS). Three further articles concentrated on metabolic homeostasis, acid–base status, energy expenditure and gastrointestinal motility; and the two final articles report studies concerning basic supportive measures (that is, fluid resuscitation and the control of shivering during core temperature reduction).

Macrocirculation and microcirculation during shock: impact of arginine vasopressin, erythropoietin and nitric oxide

Low-dose AVP infusion is increasingly used to treat sepsis-related vasodilatation and to decrease vasopressor requirements in patients with refractory septic shock. The encouraging effects of low-dose AVP infusion – such as restored vascular tone, increased blood pressure, reduced catecholamine needs, and improved renal function reported in animal studies – however, are counterbalanced by data on adverse events related to a markedly reduced systemic blood flow

and oxygen transport [1]. Furthermore, despite a reduced mortality in a subgroup of patients with less severe septic shock, low-dose AVP did not improve the outcome in the recently published Vasopressin versus Norepinephrine in Septic Shock Trial (VASST) when compared with the standard-treatment control group receiving noradrenaline [2]. Any safety issue possibly limiting the clinical use of AVP is therefore a matter of concern [3]. In this context, the effect on hepatosplanchnic blood flow assumes particular importance given its possibly crucial role for both the initiation and aggravation of sepsis.

Krejci and colleagues investigated the effect of low-dose AVP on the microcirculation and regional blood flow during early, short-term, normotensive and normodynamic fecal peritonitis-induced porcine septicemia [4], a study complementary to their simultaneous report on the effects on the gastrointestinal circulation [5]. AVP (0.06 IU/kg/hour) reduced the liver blood flow, mainly due to a decrease in portal venous flow, and reduced microcirculatory perfusion in the pancreas. Renal macrocirculatory and microcirculatory perfusion decreased as well, while the urine output remained unaffected – most probably as a result of the increased blood pressure. While the rise in hepatic arterial flow most likely reflects the well-maintained hepatic arterial buffer response already shown for terlipressin during long-term, hyperdynamic porcine endotoxemia [6], the overall data reported by Krejci and colleagues are in contrast with previous reports in well-resuscitated shock models characterized by a sustained increase in cardiac output [6,7]. Based upon their findings the authors concluded that the clinical use of AVP should be cautioned. An accompanying commentary underscored the crucial importance of the experimental design, concluding it mandatory to transfer experimental data on AVP infusion in shock models into the clinical scenario – that is, the duration, the underlying hemodynamic status, the necessity of adequate fluid

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AVP = arginine vasopressin; EPO = erythropoietin; IL = interleukin; iNOS = inducible nitric oxide synthase; NO = nitric oxide.

resuscitation and the strict adherence to low-dose infusion regimens demonstrated to be safe by other research [8].

In addition to septic shock, uncontrolled hemorrhagic shock is a primary focus of the research on AVP. The main objective during resuscitation from severe hemorrhage comprises increasing oxygen delivery to vital organs without concomitant augmentation of bleeding. Current guidelines for hemodynamic stabilization of critically injured patients with uncontrolled hemorrhage recommend fluid administration, while there is an ongoing debate on the time involved and the volume and type of fluid solutions used [9,10]. Vasopressors also allow restoration of blood pressure, while limiting the amount of volume infused, and several experimental studies and individual case reports have shown promising effects of AVP under these circumstances [11-13]. The putative advantage of AVP over fluid resuscitation alone in this context relates to its potent vasoconstrictive properties, resulting in increased coronary and cerebral perfusion pressure as well as a redistribution of cardiac output to these organs at the expense of the skeletal muscle, cutaneous and splanchnic vascular beds, thus consecutively increasing vital organ perfusion and reducing further blood loss, even in severe acidosis and distinct vasoplegia [11].

To clarify the possible impact of AVP on hemodynamics and short-term survival during potentially lethal hemorrhage, Stadlbauer and colleagues compared AVP infusion with fluid resuscitation and a saline placebo during abdominal vascular injury and subsequent hemorrhagic shock in swine. When the mean arterial blood pressure decreased below 20 mmHg due to a blood loss of 2 l, either AVP (bolus, 0.4 IU/kg; following infusion, 0.08 IU/kg/min) or fluid resuscitation (25 ml/kg lactated Ringer's solution and 25 ml/kg gelatine solution) was initiated. All untreated control animals died within 15 minutes. While initially the mean arterial blood pressure increased with both treatments, it subsequently decreased more rapidly in the fluid resuscitation group due to a higher total blood loss, which resulted in death in all but one animals in that group within the first 30 minutes before surgical intervention and supplementary fluid therapy could be started. The authors therefore persuasively repeated their previous results in an uncontrolled hemorrhagic shock model due to liver trauma [11,14]. Nevertheless, as the authors correctly mention, data are lacking on regional blood flow, visceral organ function and integrity, and the authors also highlight the ambiguity of their results with respect to neurological function or long-term survival. Consequently, the advantage of the AVP treatment alone during uncontrolled hemorrhage has to be investigated in comparison with a fluid–vasopressor combination – in particular because another experimental study in porcine liver damage-induced uncontrolled hemorrhage did not show any superior effect of AVP compared with noradrenaline when combined with small-volume resuscitation [15].

Based upon its stimulating effect on erythroid progenitors within the bone marrow, EPO is predominantly used to treat anemia in various clinical settings and thus to reduce the need for blood transfusions [16]. In addition, despite unchanged transfusion requirements, a recently published study on the use of EPO in critical illness showed an unexpected mortality benefit [17], which was referred to protective nonhemopoietic properties [18]. In fact, EPO – a type I cytokine with antiapoptotic functions – was demonstrated to reduce systemic inflammation and/or organ injury in several preclinical shock models [19]. In particular, EPO is protective for many organs after ischemia/reperfusion, among which the brain, the heart and the kidney seem to be the most promising targets [18]. Such a protective effect has already been shown in patients after acute ischemic stroke [20], and was recently confirmed for the kidney and the spinal cord in a clinically relevant model of porcine thoracic aortic occlusion mimicking surgery for thoracic aortic aneurysm [21]. In this model EPO also reduced the vasopressor requirements needed to maintain blood pressure during the early reperfusion period, thus also suggesting a beneficial effect on vasoconstrictor responsiveness.

In the context of vasoconstrictor properties of EPO due to direct effects on smooth muscle cells and increased circulating levels of endothelin-1, Kao and colleagues investigated the effect of EPO (400 U/kg; that is, doses similar to those used to reduce transfusion needs in critically ill patients [16]) on skeletal muscle capillary perfusion and tissue oxygenation 18 hours after induction of murine sepsis with cecal ligation and puncture [22]. While EPO did not affect the systemic hemodynamics or lactate levels, the initially impaired microcirculatory perfusion and increased bioenergetic impairment assessed by functional capillary density and by nicotinamide adenine dinucleotide fluorescence using intravital microscopy of the extensor digitorum longus muscle was restored to the levels of the sham control mice. Six hours after drug administration, the EPO-treated septic mice still presented with increased capillary perfusion, which coincided with significantly lower skeletal muscle tissue nicotinamide adenine dinucleotide fluorescence. The authors concluded that EPO improved mitochondrial oxidative phosphorylation and pyruvate metabolism as a result of attenuated tissue hypoxia due to a rapid normalization in the perfused capillary density. Nevertheless, other possible effects of EPO contributing to preserved mitochondrial integrity and subsequent enhanced oxidative phosphorylation – that is, prevention of mitochondrial membrane depolarization and cytochrome C release through antiapoptotic mechanisms [23] – may also assume importance in this context.

Nitric oxide (NO) is an important regulator of microvascular homeostasis by modifying the vascular tone, leukocyte and platelet adhesion to endothelial cells, and capillary leakage [24]. Its overproduction due to activation of the cytokine-iNOS as a response to infection, however, is thought to assume major importance in sepsis-related microcirculatory failure, contributing to organ dysfunction and failure in severe

sepsis [25]. Several nitric oxide synthase inhibitors have consequently been developed, but clinical investigations failed – probably based upon the attenuation of the protective effects of constitutive NO formation due to the use of a nonselective nitric oxide synthase inhibitor. Moreover, despite the well-established deleterious effects of its excess release, NO is known to block leukocyte adhesion and to scavenge reactive oxygen species, and thus to be an important protector for the endothelium against oxidative stress and subsequent damage [26].

In line with this rationale, preclinical investigations using selective iNOS inhibitors or iNOS-deficient mice yielded promising results [27,28]. Using a well-established and clinically relevant murine model of resuscitated hyperdynamic cecal ligation and puncture-induced sepsis, Hollenberg and colleagues investigated the impact of both genetic deletion (iNOS$^{-/-}$) and selective pharmacological inhibition of iNOS (1400W) on leukocyte dynamics and on microvascular permeability [29]. Rolling and adhesion of labeled leukocytes and leakage of FITC-conjugated albumin was assessed by intravital fluorescence microscopy in the cremaster muscle 15 to 20 hours after sepsis induction. Both genetic deficiency and pharmacological inhibition of iNOS attenuated vascular leakage, while the sepsis-related aggravation of leukocyte dynamics could not be prevented. The authors therefore concluded that iNOS activation seems to play an essential role in the modulation of vascular permeability, but that this regulation occurs independently of its action on leukocytes. Consequently, to sustain the protective effects of the constitutive NO formation, Hollenberg and colleagues suggest selective iNOS inhibition rather than nonselective nitric oxide synthase blockade [29] – although the impact of this approach remains to be elucidated in the proper clinical studies.

Metabolic studies

Metabolic acidosis is common during hemorrhagic shock, and hyperlactatemia is conventionally considered the main cause. Respecting the physicochemical fundamentals of the acid–base balance (that is, the dissociation equilibrium, the necessity of electrical neutrality, and the principle of mass conservation [30]), Bruegger and colleagues in a highly standardized canine model of hemorrhagic shock concentrated on the profile of unmeasured anions in relation to other acid–base parameters in order to characterize the potential contributors to the unmeasured anions [31]. In addition to the traditional parameters used to identify the presence of unmeasured anions (for example, the anion gap and the strong ion difference), the strong ion gap was calculated. The strong ion gap is defined as the difference between the apparent strong ion difference, derived from measuring strong cations and anions and summing their charges, and the effective strong ion difference, which is estimated from the carbon dioxide partial pressure and the concentrations of the weak acids (for example, albumin, phosphate) [32]. In the current study, both the anion gap and

the strong ion gap increased after the induction of shock, which was associated with significantly increased lactate, citrate, acetate and urate serum levels, measured with the help of capillary electrophoresis [31]. While not detectable at baseline, fumarate and α-ketoglutarate were both found in all animals from the induction of shock until the end of the experiment. The authors concluded that mitochondrial dysfunction may be responsible for their finding, since acetate, coupled with coenzyme A, is normally consumed during Krebs cycle in the mitochondria, and citrate, fumarate and α-ketoglutarate represent intermediate substrates of this cycle [33].

Although direct proof of mitochondrial dysfunction and its correlation with the strong ion gap is not yet available, Bruegger and colleagues' findings support the concept of early mitochondrial dysfunction and energy debt during hemorrhagic shock: in fact, in critically ill patients, the strong ion gap was a strong predictor of mortality if it was the major source of metabolic acidosis [34]. Consequently, strategies decreasing cellular energy expenditure by modulating mitochondrial respiration [35], such as cooling down [36] or hydrogen sulfide-induced suspended animation [37], may prove beneficial in hemorrhagic shock. Although the impact of fluid resuscitation on the acid–base status must not be overlooked [38], the strong ion gap might present an attractive bedside parameter in critical illness resulting from hemorrhagic shock, based on the assumption that it is indeed directly related to the degree of mitochondrial dysfunction in hemorrhagic shock.

Disturbed gastric motility and delayed gastric emptying is a common phenomenon in critical illness [39]. Several factors seem to be associated with feeding intolerance and dysmotility of the gastrointestinal tract, such as admission diagnosis and ongoing therapy with sedatives and/or catecholamines [40,41], but although our understanding has markedly improved in recent years, the precise mechanisms remain unclear [42]. It is well established that plasma concentrations of cholecystokinin and peptide YY plasma levels are elevated in fasted states as well as in anorexia nervosa or malnutrition. Nguyen and colleagues studied the relation between peptide YY and cholecystokinin concentrations and gastric emptying in 39 mechanically ventilated intensive care unit patients, two-thirds of whom presented with delayed gastric emptying as assessed with the ^{13}C-octanoate breath test [43]. Plasma cholecystokinin and peptide YY concentrations were significantly higher in these latter patients both at baseline and after gastric feeding. Furthermore, while fasting and postprandial cholecystokinin and peptide YY plasma levels and gastric emptying were inversely related, the feeding-induced rise of the blood concentrations of these two hormones was directly related to gastric emptying.

The latter finding is complementary to a simultaneous report from the authors' group that baseline and duodenal feeding-

induced plasma cholecystokinin levels are higher in critically ill patients than in healthy control individuals [44]. The authors suggest there is a complex interaction between hormonal release, nutrients and gastric emptying, and consequently they emphasize the role of enterogastric hormones in the pathogenesis of disturbed gastric emptying and gastro-intestinal passage during critical illness. This proposition may assume particular importance given the high incidence of a disturbed gastroenteral motility, which often limits enteral nutrition, while there is multiple evidence that successful early enteral feeding is associated with improved outcome in critically ill patients [45]. In this context, the assessment of gastric emptying and/or gastrointestinal passage at the bed-side remains a challenge, and at present it is unclear which $^{13}CO_2$ breath test will allow overcoming this problem [46].

It is well established that burn injury-induced mortality increases with burn size [47]. Jeschke and colleagues examined the putative association between the percentage of total body surface area burn and the inflammatory response, body composition, metabolism and organ function [48]. For this purpose, 187 severely burned children (mean age, 7 to 8 years) were divided into four groups according to burn size: total body surface area <40%, 40% to 59%, 60% to 79%, and >80%. Larger burn size was associated with a higher presence of third-degree burns, inhalation injury, ventilator dependency and number of surgical interventions, as well as with a higher incidence of infection and sepsis leading to an increased length of stay and increased mortality. While hypermetabolism, expressed as a percentage of the predicted resting energy expenditure, was present in all groups from admission to discharge, it only persisted in the two most severely burned groups. The highest serum IL-6 and IL-8 levels were seen in >80% total body surface area, most probably due to the fact that more than one-half of these patients presented with infection or sepsis.

Basic and specific therapy in critical illness
In addition to the ongoing debate of whether crystalloid or colloid solutions should be used for fluid resuscitation during critical illness, the individual qualities of the various colloid solutions have been the focus of research. Colloids are reported to have various nononcotic properties that may influence vascular integrity, inflammation and pharmaco-kinetics [49].

In a prospective clinical trial, Gombocz and colleagues therefore compared the effects of perioperative 6% dextran-70 infusion on the inflammatory response and myocardial ischemia-reperfusion injury after cardiac surgery using cardiopulmonary bypass with those of 5.5% oxypolygelatin [50]. Dextran-70 infusion was associated with lower peak plasma levels of procalcitonin, IL-8, IL-10, endothelial leukocyte adhesion molecule-1 and intercellular adhesion molecule-1, thus suggesting attenuated endothelial damage and leukocyte activation. This reduced inflammatory response

coincided with improved clinical and laboratory markers of cardiovascular function: higher stroke volume and, conse-quently, higher cardiac index, and lower peak troponin-I levels than in the oxypolygelatin-treated patients. By contrast, the postoperative drainage volume was higher in the dextran-70 group – which did not assume clinical importance, however, since neither hematocrit nor transfusion requirements significantly differed.

These authors' findings are in good agreement with experimental data that dextran-60 prevented leukocyte/ endothelial cell interaction after extracorporeal circulation, while 10% hydroxyethyl starch affected only adherent white cells [51]. Within the limits of the relatively small number of low-risk patients – rather than high-risk patients, who are probably more susceptible to benefit from these measures [52] – the study by Gombocz and colleagues adds an interesting piece to the exciting puzzle of cardiac surgery-related systemic inflammation.

Mild hypothermia represents one of the most challenging aspects of prevention of organ failure [53], since it can improve outcome but may also be associated with marked side effects [54,55]. Depending on the technical device used [56], some of the side effects limiting the initiation of hypothermia due to the inherent increase of whole body oxygen consumption are vasoconstriction and shivering. Several drugs are known to lower the thresholds for shivering or vasoconstriction, among which meperidine has been shown one of the most effective [57]. Like other opioids, however, meperidine causes sedation, and possibly respiratory depression.

Kimberger and colleagues therefore investigated the impact of a skin warming system and/or a medium dose of meperidine on thermoregulatory thresholds in healthy volunteers infused with 4°C lactated Ringer's solution to decrease the core temperature by 2.4°C/hour until shivering started [58]. Both skin surface warming and meperidine administration reduced the vasoconstriction and shivering thresholds, and combining the two approaches reduced the shivering threshold below 34°C without the occurrence of adverse effects such as respiratory depression. Combining external warming to prevent vasoconstriction with meperidine administration might therefore prove effective for the induction and maintenance of mild therapeutic hypothermia. It must be noted, however, that healthy volunteers rather than critically ill patients were studied, so any impact of disturbed neurological function, the neuroendocrine axis and/or the autonomous nervous system – either related to the disease *per se* or caused by the ongoing treatment with sedatives, catecholamines, and so forth – remains open.

Competing interests

fees from Ferring Pharmaceutical A/S (København, Denmark) for help with designing preclinical experiments. The other authors declare that they have no competing interests.

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