CRITICAL CARE

REVIEW

Year in review 2009: *Critical Care* – shock

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Abstract

The research papers on shock that have been published in *Critical Care* throughout 2009 are related to four major subjects: first, alterations of heart function and, second, the role of the sympathetic central nervous system during sepsis; third, the impact of hemodynamic support using vasopressin or its synthetic analog terlipressin, and different types of fluid resuscitation; as well as, fourth, experimental studies on the treatment of acute respiratory distress syndrome. The present review summarizes the key results of these studies together with a brief discussion in the context of the relevant scientific and clinical background published both in this and other journals.

Introduction

Thirteen original articles focusing on shock were published in *Critical Care* in 2009. Two papers concentrated on the pathophysiology of heart dysfunction and its response to standard therapeutic interventions, and three other studies concentrated on the role of pharmacological inhibition of the sympathetic central nervous system during sepsis using either central sympatholytics or thoracic epidural blockade. Five articles concentrated on the (side) effects of arginine vasopressin and its analog terlipressin on the heart and the visceral organs, and on the question of which type of solution fluid is most appropriate for fluid resuscitation. Three final studies investigated the pharmacological interventions in experimental models of acute respiratory distress syndrome (ARDS). The present review summarizes the key results of these studies and discusses them in the context of the relevant scientific and clinical background, in particular highlighting the relation to studies published in this journal as well as in other journals during this period.

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Pathophysiology of heart function

By definition, septic shock comprises systemic vasodilatation and consecutive arterial hypotension despite increased cardiac output. Approximately 40% of these patients also develop myocardial dysfunction, which is characterized by reduced systolic contractility, impaired diastolic relaxation and – in some patients – ventricular dilatation [1,2]. Since aggressive fluid resuscitation is one of the cornerstones of the hemodynamic management of patients with septic shock, diastolic dysfunction may assume particular importance. The frequency-dependent acceleration of relaxation is one of the physiological mechanisms to maintain adequate ventricular filling at increased heart rates, and therefore Joulin and colleagues tested the hypothesis of whether endotoxin (lipopolysaccharide) may impair the cardiac force–frequency relationship [3]. In cardiomyocytes *in vitro*, as well as in an *ex vivo* isolated heart preparation, lipopolysaccharide blunted the otherwise marked drop in the diastolic time constant. *In vivo*, echocardiography showed a reduced early diastolic mitral annulus velocity, suggestive of impaired left ventricular diastolic relaxation. Disturbed sarcoplasmatic Ca^{2+} homoeostasis and increased serine/threonine phospatase activity were responsible for this diastolic dysfunction. The authors concluded that the disruption of this fundamental mechanism ensuring adequate cardiac filling may be particularly detrimental during septic shock, which is commonly associated with tachycardia and dependence on increased preload.

The article by Joulin and colleagues was accompanied by an editorial commentary from Heitner and Hollenberg highlighting the importance of the sarcoplasmic reticulum Ca^{2+}-ATPase in this context, and at the same time emphasizing that there are also other important mediators of adequate diastolic function [4]; for example, nitric oxide (NO) [2]. In fact, in a murine model of well-resuscitated septic shock resulting from cecal ligation and puncture (CLP)-induced peritonitis, Barth and colleagues showed that both genetic deletion and selective pharmacologic blockade of the inducible isoform of the NO synthase (iNOS, NOS2) was associated with markedly improved systolic contraction and catecholamine responsiveness, but simultaneously deteriorated diastolic relaxation [5]. Furthermore, Bougaki and colleagues most recently demonstrated the crucial role of

the endothelial isoform of the NO synthase (NOS3) for the maintenance of heart function in sepsis: colon ascendens stent peritonitis-induced septic shock caused a more pronounced depression of both systolic contraction and diastolic relaxation in NOS3-knockout mice than in the wild-type strain [6].

Sedation is frequently necessary in patients with septic shock, and therefore Zausig and colleagues investigated the effects of dose-dependent effects of various induction agents (propofol, midazolam, s(+)-ketamine, methohexitone, etomidate) in a Langendorff heart preparation from rats rendered septic by CLP [7]. Propofol exerted the most pronounced depressant effects on both the maximal systolic contraction and the minimal diastolic relaxation, and cardiac work. Furthermore, propofol only adversely deleteriously affected the myocardial oxygen supply–demand ratio. In contrast, s(+)-ketamine was associated with the best maintenance of cardiac function. Within the limits of the study – that is, the use of an *ex vivo* isolated organ model – the authors concluded that s(+)-ketamine may be an alternative to the comparably inert etomidate, the use of which is, however, limited due to its endocrine side effects [8].

The study by Zausig and colleagues was accompanied by an editorial commentary from Royse highlighting both the merits as well as the pitfalls of the study [9]; for example, the lack of an analysis of the effects of volatile anesthetics, which are known to promote protective preconditioning during conditions of ischemia–reperfusion, particularly in the heart. Most recently, the study by Zausig and colleagues on induction agents was complemented by the analysis of the effects of the inotropes dobutamine, dopamine, epinephrine, and levosimendan in the same model, thus giving an overview of the cardiac effects of drugs most commonly used for the management of patients with septic shock [10].

The sympathetic central nervous system in sepsis

The autonomic nervous system is referred to as an important regulator of the immune system due to its capacity for modulating the production of proinflammatory cytokines by immune cells. While catecholamines exhibit a friend and foe character [11], acetylcholine – the key mediator of the cholinergic anti-inflammatory pathway – can directly inhibit cytokine activation via the α_7 subunit of the nicotinic acetylcholine receptor expressed on macrophages, and thus can dampen the inflammatory response [12].

Administration of central α_2-agonists allows lowering sympathetic tone due to stimulation of central α_2-receptors and consecutive inhibition of noradrenergic neurotransmission in the medulla oblongata. As a logical consequence of a previous experiment using cholinesterase inhibition with physostigmine [13], Hofer and

colleagues investigated the effect of the central α_2-receptors clonidine and dexmedetomidine in a murine model of CLP-induced sepsis [14]. Both drugs improved survival, which was associated by a markedly attenuated release of the proinflammatory cytokines IL-1β, IL-6 and TNFα as well as reduced activation of the nuclear transcription factor NF-κB. Since clonidine did not affect cytokine release in blood stimulated with lipopolysaccharide *ex vivo*, the central nervous effect was responsible for its beneficial properties. It is noteworthy, however, that this protective effect was only present after pre-emptive drug injection (that is, using a pretreatment design), whereas drug administration as early as 1 hour after induction of CLP had no effect. The accompanying editorial comment from Ulloa and Deitch [15] emphasized this issue as a putative consequence of high concentrations of circulating catecholamines that can boost the initial inflammatory response during the early phase of sepsis, the possibly confounding role of ketamine anesthesia as well as the lacking antibiotic treatment in the model by Hofer and colleagues.

Thoracic epidural anesthesia (TEA) using local anesthetic is associated with regional sympathetic blockade. Two complementary studies by Lauer and colleagues and by Freise and colleagues therefore respectively addressed the question of whether TEA may beneficially influence the pulmonary microcirculatory perfusion [16] and hepatic microcirculatory perfusion [17] in rats with CLP-induced sepsis. To differentiate between hyperdynamic and hypodynamic sepsis, Lauer and colleagues assessed the effects of TEA both 6 and 24 hours after the CLP procedure. Finally, an isolated lung preparation allowed the authors to clarify the mechanisms of a possible impact of TEA on pulmonary endothelial dysfunction. TEA exerted marked anti-inflammatory properties by reducing the amount of exhaled NO during both hyperdynamic and hypodynamic sepsis and, moreover, reduced neutrophil influx into the lungs in the hypodynamic phase. Interestingly, this anti-inflammatory effect reduced endothelial dysfunction only during hyperdynamic sepsis, whereas it even aggravated endothelial function in the hypodynamic phase [16]. In addition, Freise and colleagues showed that TEA normalized the sepsis-related hepatic sinusoidal blood flow, most probably as a result of a restoration of the otherwise impaired hepatic arterial buffer response, and ameliorated the leukocyte adhesion to the endothelium [17]. The two articles represent the logic consequence of previous experiments by the authors' group both in rodents [18,19] and in sheep [20], and thus add further pieces to the puzzling debate on the use of TEA during sepsis. Clearly, there is traditional reluctance against this approach [21], but the existing experimental data [22,23] and clinical data [24] should foster its thorough evaluation.

Hemodynamic support

Vasopressin and terlipressin

Despite the lack of improvement for mortality in the Vasopressin in Septic Shock Trial (VASST) study [25], and although worsened mortality and morbidity were recently reported in children [26] and in trauma patients [27], arginine vasopressin (AVP) and its analog terlipressin are increasingly used to restore blood pressure during vasodilatory shock. The increase in blood pressure is mainly due to systemic vasoconstriction, and thus may lead to a drop in coronary blood flow despite increased coronary perfusion pressure. These drugs, despite some encouraging data in patients with cardiogenic shock [28], may therefore carry the risk of inducing myocardial ischemia in patients with underlying cardiac pathology. In fact, the VASST study explicitly excluded patients with cardiogenic shock, congestive heart failure, and unstable coronary artery disease.

Consequently, Indrambarya and colleagues compared a 72-hour infusion of AVP (infusion rate equivalent to 0.04 IU/minute in a 70 kg human being), dobutamine (8.33 µg/kg/minute) and vehicle in a murine model of cardiac ischemia [29]. At day 1 and day 3 after coronary ischemia, echocardiography demonstrated a more pronounced fall in left ventricular ejection fraction than in the vehicle-treated and dobutamine-treated animals, which ultimately coincidence with a nearly doubled mortality in the AVP group. The authors attributed this higher mortality to sudden cardiac arrhythmias caused by the K_{ATP}-channel blocking properties of AVP, and concluded that the use of AVP should be cautioned in patients with underlying cardiac disease.

The accompanying editorial highlighted the complex effects of AVP on cardiac function, which relate to both direct and indirect mechanisms [30]. In fact, AVP markedly decreased systolic contractility in swine after transient myocardial ischemia in a dose-dependent manner [31] as a result of a coronary vasoconstriction-related reduction in coronary flow [31,32] that ultimately led to myocardial ischemia. Weig and colleagues showed enhanced cardiac contractility after vasopressin receptor 2 gene transfer [33], however, and Ryckwaert and colleagues demonstrated that the terlipressin-induced coronary hypoperfusion was only present under constant pressure, not under constant flow conditions [34]. Moreover, Simon and colleagues compared AVP with a standard treatment with noradrenaline during long-term, resuscitated porcine fecal peritonitis-induced septic shock, and AVP attenuated the otherwise progressive increase in troponin I [35]. In their study, AVP also compared favorably with noradrenaline with respect to liver injury and, in particular, renal function. Again, nothing is simple and easy when transferring experimental findings to the clinical setting. While

Gordon and colleagues most recently reported in a *post hoc* analysis of the VASST study that AVP reduced progression to renal failure in patients with septic shock and acute kidney injury [36], other authors have shown that vasopressin impaired intestinal mucosal perfusion and renal oxygenation after cardiac surgery [37,38].

Although both AVP and terlipressin exert vasopressor properties, distinct pharmacokinetic differences as well as pharmacodynamic differences between these two drugs must be taken into account: the half-life of terlipressin is 4 to 6 hours (vs. 20 minutes for AVP), and it has a nearly threefold higher selectivity for the vasopressin receptor 1a, which might theoretically result in less vasopressin receptor 2-mediated side effects (for example, anti-diuresis and activation of coagulation) [39]. Morelli and colleagues therefore performed the Continuous Terlipressin Versus Vasopressin study, the first clinical study to compare the effects of continuous intravenous AVP (0.03 IU/minute) and terlipressin (1.3 µg/kg/hour; that is, approximately 2.5 mg/day) with noradrenaline (15 µg/minute) in the control arm (n = 15 in each group) [40]. In addition to these fixed infusion rates, all patients received open-label noradrenaline as needed to achieve the target blood pressure of 70 ± 5 mmHg. Whereas terlipressin allowed for a much more pronounced reduction in open-label noradrenaline requirements, none of the parameters of hemodynamics, gas exchange, metabolism or organ function showed any significant intergroup difference [40].

The editorials accompanying the studies by Simon and colleagues and by Morelli and colleagues emphasized the possible limitation of these investigations related to the use of fixed doses of the drugs that are supplemented by noradrenaline, and furthermore highlighted the potential of AVP or terlipressin as a first-line vasopressor rather than as a last-resort therapy [41,42]. In this context, the study by Rehberg and colleagues on the use of AVP and terlipressin in ovine septic shock induced by fecal peritonitis assumes particular importance: terlipressin but not AVP was associated with less fluid requirements to maintain constant hematocrit levels, and ultimately prolonged survival [43]. The concept of using AVP or terlipressin is also of interest when taking into account the results of the VASST study: in fact, despite an overall comparable outcome, the mortality in patients with less severe septic shock was significantly lower in the vasopressin group than in the noradrenaline control group [25], suggesting that an early intervention with noncatecholaminergic vasopressors may increase survival from septic shock.

Fluid resuscitation

Fluid resuscitation is one of the cornerstones of the treatment of patients in the intensive care unit, particularly

for the prevention and management of acute kidney injury [44], and safety issues of the solutions used therefore assume major importance. It is well established that hydroxyethyl starch (HES) can induce kidney injury [45,46], but it is still a matter of debate whether the various HES preparations have different nephrotoxic properties [47,48]. Even clinical studies have yielded equivocal results: a third-generation balanced 6% HES 130/0.42 plus crystalloid solution was associated with less acidosis, systemic inflammation and lower neutrophil gelatinase-associated lipocalin blood concentrations than a nonbalanced HES solution combined with saline [49]; and the incidence of acute kidney injury was similar in surgical intensive care unit patients receiving a predominantly HES-based or gelatin-based fluid therapy [50].

Hüter and colleagues therefore compared a second HES preparation (10% HES 200/0.5) and 6% HES 130/0.42 with a balanced crystalloid solution in a porcine isolated renal perfusion model [51]. After hemodilution *in vivo*, the glomerular filtration pressure and creatinine clearance were higher in the crystalloid control group. The 10% 200/0.5 HES solution caused a more severe drop in creatinine clearance than the third-generation preparation, which was associated with more pronounced macrophage infiltration and tubular damage. This latter effect was independent of the filtration pressure, which was identical in the two HES groups. Most recently, Schick and colleagues confirmed these nephrotoxic properties of HES in rats with CLP-induced sepsis: despite a significantly higher cardiac output, HES and gelatine were associated with a more severe histological tissue injury and higher neutrophil gelatinase-associated lipocalin serum levels than treatment with normal saline or balanced crystalloid solutions [52]. These results confirm the warnings raised in a recent review on this topic [53].

An accompanying editorial highlighted the fact that third-generation HES preparations may lead to comparable kidney injury as older compounds [54]. In the absence of large randomized, controlled clinical trials, doubts on the safety of HES therefore remain due to the evidence that certain colloids, particularly in high amounts, may cause harm in different organ systems. Furthermore, despite the ongoing debate on the optimal solution for fluid for resuscitation, there is little to no evidence that colloids improve outcome in critically ill patients, and thousands of patients included in randomized controlled trials have been safely resuscitated using only crystalloids [55].

Nevertheless, Hiltebrand and colleagues showed that, after major abdominal surgery in pigs, goal-directed therapy (targeting a mixed venous hemoglobin oxygen saturation >60%) combining lactated Ringer's solution (3 ml/kg/hour) with HES boluses compared favorably

with lactated Ringer's solution alone in restoring mesenteric microcirculation and macrocirculation and metabolism [56]. It is noteworthy, however, that the parameters of intestinal metabolism (mesenteric acid–base status, lactate levels) did not show major benefit. Furthermore, the authors' experiments comprised an observation period of only 4 hours, and data on perfusion or renal function were not recorded. The study by Hiltebrand and colleagues emphasizes the crucial importance of the underlying pathology: in pigs challenged with endotoxin or rendered septic by fecal peritonitis, a high-volume fluid resuscitation (15 ml/kg/hour Ringer's lactate plus 5 ml/kg/hour HES) increased mortality despite a better initial hemodynamic stability when compared with a moderate-volume approach (10 ml/kg/hour Ringer's lactate) [57].

Finally, in a porcine model of short-term, partially resuscitated hemorrhagic shock, Phillips and colleagues demonstrated without using colloids that the type of crystalloid solution used assumes particular importance: when compared with normal saline, lactated Ringer's solution improved the extravascular lung water, acid–base status and mean arterial blood pressure, but not oxygenation, when the total amount of fluid did not exceed 250 ml/kg [58]. The authors tried to mimic the prehospital and early clinical resuscitation phase of hemorrhagic shock and resuscitation, which may explain the discrepancy from the data reported by van der Heijden and colleagues: these authors did not find any difference in extravascular lung water or the lung injury score after 90 minutes of fluid loading for hypovolemia with NaCl 0.9%, gelatin 4%, HES 6%, or albumin 5%, no matter whether the patients were septic or not [59].

Pharmacological interventions in experimental ARDS

There is ample experimental evidence that β_2-agonists may represent an adjunct therapy in the management of ARDS due to reduced pulmonary neutrophil sequestration and activation, increased alveolar fluid clearance, enhanced surfactant secretion, and modulation of the inflammatory and coagulation cascade [60]. Moreover, the recent Beta-Agonist in Acute Lung Injury Trial on the effects of intravenous 15 µg/kg/hour salbutamol showed a significant decrease in extravascular lung water and airway plateau pressure in the treatment group at day 7, which ultimately resulted in a trend towards lower Murray ARDS scores [61] – one of the mechanisms being the upregulation of matrix metalloproteinase-9 in type II alveolar cells [62]. Except for a slightly higher incidence of new-onset supraventricular arrhythmia, the treatment was well tolerated. By contrast, the Albuterol for the Treatment of ALI Trial did not show significant improvement of ventilator-free days or mortality [63]. These

heterogeneous results might be related to the cardio-vascular side effects of β_2-agonists; for example, an increased cardiac output.

This question of the role of β_2-agonists was addressed by Briot and colleagues [64], who measured the time-course of capillary-alveolar leakage of macromolecules (fluorescein-labeled dextran) in a canine model of oleic acid-induced acute lung injury. Oleic acid increased the capillary-alveolar leakage, and infusing terbutaline infusion further enhanced the macromolecule leakage, which coincided with significantly increased cardiac output and pulmonary artery pressure. The authors speculated that the increased blood flow caused recruitment of leaky pulmonary capillaries, which in turn would aggravate overall lung endothelial permeability. These findings agree with data from Schreiber and colleagues demonstrating that a dobutamine-induced increase in pulmonary blood flow in rats with unilateral, left lung acid instillation increased lung edema as well as inflammatory cell infiltration and histopathologic damage in the contralateral, unaffected organ [65]. Consequently, the question of the role of β_2-agonists in ARDS remains unanswered [63].

The accompanying editorial comment emphasized one of the most important issues in this context: pharmacological monotherapy is unlikely to simultaneously address the various interactions between different pathophysiological pathways in ARDS [66]. This phenomenon might also limit the use of recombinant human activated protein C (rhAPC) for the treatment of ARDS. While there is ample evidence from large animal models that infusing rhAPC can improve lung function and attenuate morphological organ injury [67-71] as a result of reduced tissue inflammation and oxidative stress [72], a randomized clinical trial in patients with acute lung injury failed to show any benefit of this treatment [73]. The latter study was limited to patients with acute lung injury rather than ARDS, and hence to patients with a reduced risk of bleeding.

Since intravenous rhAPC is known to increase bleeding complications, Waerhaug and colleagues tested the hypothesis of whether aerosolized rhAPC might improve lung function in their well-established model of oleic acid-induced ovine acute lung injury [74]. Inhaled rhAPC improved arterial oxygen partial pressure as a result of reduced intrapulmonary shunt perfusion, which was associated with significantly larger volumes of aerated lung tissue. Inhaled rhAPC did not, however, prevent the increase in extravascular lung water nor the lipopolysaccharide-induced acute pulmonary hypertension [74]. Nevertheless, the findings by Waerhaug and colleagues are complementary to data reported by Finigan and colleagues: treatment with intravenous rhAPC started either before or at 30 and 150 minutes after initiating injurious mechanical ventilation (tidal volume, 20 ml/kg) in mice marked attenuated pulmonary vascular leakage [75]. Finally, Maniatis and colleagues demonstrated most recently that inhaled rhAPC is equally effective under these conditions [76]. In the accompanying editorial, Liu and colleagues emphasized the potential value of this innovative approach for the use of rhAPC, but also highlighted the fact that the response of arterial oxygen partial pressure to therapeutic interventions is not related to mortality of ARDS and, hence, the question of whether inhaled rhAPC may improve outcome in these patients remains open [77].

Nosocomial infection with methicillin-resistant *Staphylococcus aureus* (MRSA) represents a particular problem in intensive care units, both due to the budget and personnel burden [78] as well as due to the epidemiology and virulence of the bacterial strain [79]. Enkehbaater and colleagues therefore established a novel ovine model of MRSA-induced ARDS, which results from a double-hit challenge comprising smoke injury and MRSA installation into the airways [80] and is character-ized by circulatory collapse and vascular hyperpermea-bility [81].

Excess NO production and formation of reactive nitrogen species (for example, peroxynitrite) are attri-buted to assume crucial importance in the pathophysio-logy of ARDS [82]. Jonkam and colleagues therefore tested the hypothesis of whether excess NO and/or reactive oxygen species production is also responsible for the lung injury induced by MRSA pneumonia [83]. In fact, after smoke injury and instillation of MRSA, ewes showed markedly increased tissue expression of both iNOS and endothelial NO synthase, which was associated with significantly higher blood nitrate and nitrite concentrations. In addition, the tissue polyADP ribose levels were significantly elevated. In this context, a most recent article by Su and colleagues deserves particular attention: in an ovine model of fecal peritonitis-induced septic shock, these authors compared a highly iNOS-selective NO synthase blocker with noradrenaline and the combination of these two compounds. Both with or without additional noradrenaline, animals treated with the selective iNOS blocker showed less pulmonary artery hypertension and gas exchange impairment and higher visceral organ blood flow [84]. Taken together, the findings in these clinically relevant large animal models raise again the question of (selective) iNOS inhibition in sepsis [85,86].

Abbreviations

ARDS, acute respiratory distress syndrome; AVP, arginine vasopressin; CLP, cecal ligation and puncture; HES, hydroxyethyl starch; IL, interleukin; iNOS, NOS2 inducible nitric oxide synthase; K_{ATP}, ATP-dependent potassium; MRSA, methicillin-resistant *Staphylococcus aureus*; NF, nuclear factor; NO, nitric oxide; rhAPC, recombinant human activated protein C; TEA, thoracic epidural anesthesia; TNF, tumor necrosis factor; VASST, Vasopressin in Septic Shock Trial.

Competing interests

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