Blood pressure is crucial for the tissue perfusion, oxygenation and elimination of metabolites in normal tissue. In septic patients it may be altered by several mechanisms. Endothelial lesions and impaired vasoregulation resulting from bacteremia may produce vasodilatation, hypotension, tissue hypoxia and decrease in the blood velocity. These events may favour disseminated intravascular coagulation in septic patients, and thus pronounce perfusion misdistribution. Since hypotension is commonly treated by vasoactive drugs to increase vascular tone toward normal values, more pronounced peripheral tissue ischemia may result. During the process of blood pressure regulation in septic patients a diversity of physiological parameters should be encountered, i.e. age, body weight, core temperature, overall patients’ cardiovascular performance, anemia, and protein status. In a healthy, adult person, in the absence of other causes of hypotension systolic blood pressure of > 90 mmHg or mean arterial pressure ≥ 70 mmHg should maintain adequate tissue perfusion. Together with specific antibiotics, therapeutic procedures like haemodilution, use of vasoconstrictors, vasopressin and its analogue terlipressin, corticosteroids are currently used to improve outcome of hypotensive septic patients. Numerous studies were undertaken to point the values of the biochemical tests suggesting a need for prompt intervention. The arterial lactate, cortisol response, TNF, interleukin (IL) 6, IL-12p70 and IL-12p40 production, together with submucosal (gastric intramucosal or sublingual) CO2 values were proven as indicative. These may suggest whether microcirculatory impairment is reversible or not, and which therapeutic maneuver should be appropriate.

Key words: sepsis, shock, blood pressure, vasoconstrictor agents
INTRODUCTION

Sepsis is characterized by the reduction in the peripheral vascular tone on both the arterial and venous sides of the circulation and impaired oxygen utilization resulting in the elevated lactate levels, and varying degree of organ dysfunction. Early ‘warm’ phase is recognized by vasodilation, acidosis, fever, tachycardia, tachypnoea, respiratory alkalosis and an increased cardiac output with warm, dry peripheries (1). Advanced sepsis presents with the signs of organ failure: myocardial contractile dysfunction with low cardiac output, progressive acidosis, respiratory failure, clammy peripherally shut down, and with progressive neurologic disorder. Late or ‘cold’ sepsis is characterized by vascular hypo-reactivity, multiple organ dysfunctions with profound acidosis and frequently death (1).

Microvascular impairment and blood pressure (BP) regulation are crucial for the outcome of septic patients, being in the same time a marker of the disease severity and progression, and predictor of the treatment efficiency. This paper presents a diagnostic and therapeutic approach to the BP regulation in the severe sepsis and septic shock.

PATHOPHYSIOLOGY

Three integrated components of severe sepsis are: infection with systemic activation of inflammation, activation of coagulation and impairment of fibrinolysis (2).

During the development of sepsis, various proinflammatory cytokines are released, such as endotoxin-induced tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6). These proinflammatory cytokines induce endothelial injury and vascular bed-specific changes (2). The endothelial damage and increased thrombogenicity are linked to the development of the clinical signs of sepsis (2, 3). Inflammatory changes trigger the extrinsic coagulation pathway, which is mostly subclinical, but can be observed in the commonly measured haemostatic parameters (4). The most deleterious form of the haemostatic system activation in sepsis is the disseminated intravascular coagulation. It is characterized by coagulation activation on the activated endothelium and subsequent bleeding, as a resultant of coagulation factors consumption (4). In the sepsis normal fibrinolytic response is suppressed by fall in plasminogen levels while antiplasmin levels remains normal and thrombin-antithrombin (TAT) complexes increases (4). Typically, tissue factor expression is increased in a subset of endothelial cells and plasminogen activator inhibitor-1 is released and impairs fibrinolysis (2, 3). Fibrinolysis is further impaired by the generation of increased amounts of thrombin-activatable fibrinolysis inhibitor (TAFI) (4). Although plasminogen/antiplasmin ratio and plasminogen activator inhibitor-1 (PAI-1) levels remain abnormal in non-surviving patients, they tend to normalize in survivors (4).

The endothelial cell is the central point of interactions between the inflammatory events and disturbed hemostasis in patients with severe sepsis (3, 4, 5). Endothelial cell injury or death can shift the cell’s phenotype to prothrombotic and induce sequestration of inflammatory cells and platelets in the damaged vessels. The resulting microvascular flow obstruction produces acute organ dysfunction with hypoperfusion/ischemia and can ultimately lead to death (4).

SEPSIS RESULTS IN DOWN-REGULATION OF ADRENERGIC RECEPTORS

Recent study investigating the role of adrenergic system in sepsis showed that the pressor effect of norepinephrine was markedly diminishing during endotoxemia (5). Endotoxemia causes a systemic down-regulation of alpha1-receptors on the level of gene expression and suggest that this effect is likely mediated by proinflammatory cytokines in a synergistic but nitric oxide-independent fashion. This down-regulation of alpha1-adrenergic receptors contributes to the attenuated BP response to norepinephrine and, therefore, to circulatory failure in septic patients (5). Furthermore, study by Bernardin et al demonstrated that patients with
severe sepsis or septic shock had postreceptor defects of the beta-adrenergic signal transduction. This finding suggests a heterologous desensitization of adenylate cyclase stimulation (6). Also, the serum of patients with sepsis contains soluble depressant substances that inhibited adenyl cyclase activation by beta-adrenergic agonists. Hyperactivation of the Gi pathway of adenyl cyclase was mainly responsible for the altered transmembrane beta-adrenergic signalling (7). An impairment of beta-adrenergic signaling was observed in healthy peripheral blood mononuclear cells exposed to serum from patients with septic shock due to the involvement of the inhibitory pathway of adenyl cyclase stimulation (7). These findings could explain sometimes ineffective therapy with adrenergic agonists in septic patients (8, 9).

BIOMARKERS OF THE OUTCOME IN SEPTIC PATIENTS

Several biochemical markers like blood lactate levels, C-reactive protein (CRP), TNF, procalcitonin and lipopolysaccharide binding protein may be used as biomarkers of the sepsis severity and predictors of outcome (9, 10). Current recommendations do not support routine assessment of any laboratory markers during the sepsis treatment as indicators of disease progress and treatment efficiency, except of blood gas and lactate values. Although pH and blood lactate concentration may lack precision as a measure of tissue metabolic status, pH < 7.14 and elevated lactate levels (≥ 4 mmol L⁻¹) in the sepsis support aggressive resuscitation (8).

HEMODYNAMIC MEASUREMENTS IN THE SEPTIC SHOCK

Hemodynamic measurements are accepted as gold standards for monitoring in septic patients. The pulmonary artery flotation catheter is currently replaced with less invasive monitoring methods, such as PICCO (pulse contour cardiac output), LIDCO (lithium dilution cardiac output), and transcutaneous oxygen pressure monitoring (1, 8, 9). Mixed venous oxygen saturation is a useful surrogate for the cardiac index (CI) as a target for hemodynamic therapy in adult population (8, 9). In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation (9).

Measurement of cardiac output and oxygen consumption are reliable predictors of the sepsis outcome in children with septic shock (11). American College of Critical Care Medicine has provided clinical guidelines for hemodynamic support of neonates and children with septic shock, and identified the critical values of hemodynamic parameters that were associated with improved survival. CI between 3.3 and 6.0 L/min/m² and oxygen consumption >200 mL/min/m² are identified as predictive factors. With hemoglobin concentration of 10 g dL⁻¹ and 100% arterial oxygen saturation, the CI of >3.3 L/min/m² correlates to a mixed venous oxygen saturation of >70% (11).

A SCORING OF MICROCIRCULATION IN THE SEPSIS

Standard non-invasive and invasive BP measurements were unable to evaluate the dynamics of microcirculation changes in the septic patients (12). In the recent years new devices have been introduced to study end organ perfusion in septic patients. Gastric tonometry alone or in the combination with laser Doppler flowmetry is currently the most widely used technique (12). The role of the diagnostic techniques that allow the microcirculation to be visualized directly is emerging. The orthogonal polarization spectral (OPS) and the sidestream dark field imaging devices provide high contrast images of capillaries and venules containing red blood cells. Different microcirculation scoring systems were reported, aimed to compare the results obtained using such devices, and to predict the outcome (12). De Backer and colleagues have proposed that scoring of the microcirculation should include: an index of vascular density, total and perfused vessel density, the perfusion index (proportion of perfused vessels), microcirculatory
flow index (MFI) and heterogeneity index (13). The persistent microvascular alterations observed using such imaging devices were more severe in nonsurvivors than in survivors, and were associated with the development of multiple organ failure (MOF) and death. They typically include decreased capillary density, and decreased perfusion of capillaries. The substantial heterogeneity in microvascular perfusion can be observed in advanced and late sepsis with microinfarctions and/or bleeding areas (Figure 1) (13). Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients dying after the resolution of shock in MOF had a lower percentage of perfused small vessels than survivors (57.4 vs. 79.3 %). Although both survivors and nonsurvivors had initial decrease in the small vessels perfusion registered at the sepsis onset, microcirculatory alterations improve rapidly in survivors but not in patients dying with MOF (10).

Using these devices, several microcirculation impairments in sepsis may be reported earlier, i.e. decrease in the gut mucosal circulation and skin hypoperfusion, arguing for specific therapies or for the discontinuation of harmful ones (14, 15). However, such devices are not widely accepted until now, and the usefulness of data obtained by these methods in the clinical decision-making is still limited (16).

Several outcome prediction systems are currently used to evaluate organ dysfunction in the intensive care unit, i.e. Sequential Organ Failure Assessment (SOFA) score, Multiple Organ Dysfunction Score (MODS) and acute physiology and chronic health evaluation (APACHE II). They may reliable predict outcome, but are not appropriate during the decision making process in the critical septic patients requiring rapid resuscitation (17).

**CRITICAL BLOOD PRESSURE VALUES IN SEPTIC PATIENTS**

The surviving Sepsis Campaign experts defined sepsis induced hypotension as a systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg or < 2 SD below normal for age in the absence of other causes of hypotension. Sepsis induced hypotension persisting despite adequate fluid resuscitation is considered as septic shock (8). As a consequence of hypotension, a persistent microvascular perfusion derangement may result in the organ failure and death (8).

Early hemodynamic interventions in the septic shock aimed at rapid normalization of arterial pressure, oxygen delivery and oxygen consumption are key factors adding to in-hospital mortality. The severity and duration of hypotension are associated with a poor outcome (9).

Target values of early goal directed therapy (EGDT) are confirmed in the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock (8, 9). The goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol: central venous pressure (CVP ) 8-12 mm Hg, systolic blood pressure...
≥90 mm Hg or MAP ≥65 mm Hg, and central venous (superior vena cava) or mixed venous oxygen saturation ≥70% or ≥65%, and urine output ≥0.5 ml kg⁻¹hr⁻¹ (8).

Blood pressure dynamic reflects vascular tone and correlates with the tissue oxygen delivery. It may parallel with biochemical markers, but in some clinical situations it is the first sign of organ function deterioration in septic patients, especially in the patients suffering from brain trauma, polytrauma or in children (11). Once the antibiotic therapy has been initiated, the hemodynamic optimization strategies targeting adjustments of cardiac preload, afterload and contractility to balance oxygen delivery with oxygen demand may substantially improve outcome (9). A significant decrease in biomarker levels was observed as early as 3 hrs for IL-1ra and ICAM-1, 6 hrs for TNF-α and caspase-3, and 12 hrs for IL-8 as a result of EGDT (17). A vascular hyporeactivity to hemodynamic supportive therapy is usually a marker of poor outcome (19).

Several mechanisms have been evoked to explain why early (but not late) hemodynamic-oriented interventions could be effective. One is that irreversible organ damage is already present when late interventions are applied, and alternative explanation may be that early interventions can attenuate the proinflammatory response, breaking a vicious cycle that could result in organ failure and death (9, 20).

The critical blood pressure value that should maintain tissue perfusion highly depends upon the patient’s physiologic performance and co-morbidities, assuring thus critical oxygen and glucose delivery (21). Comorbidities are significant factors for predicting the treatment failure in sepsis. A history of pre-existing coronary artery disease and surgical emergencies in septic patients may be associated with poor outcome (21). Patients with history of severe hypertension may furthermore require higher MAP or perfusion pressure for assuring tissue perfusion and oxygenation, whereas lower MAP may be sufficient for previously healthy young person (22).

In the haemodynamically compromised patients the values of perfusion pressure may be more appropriate for the circulation evaluation (23). Perfusion pressure is a difference between MAP and CVP (MAP-CVP). In newborns and children, lower age adjusted pressure thresholds should be considered (11), as shown on Table 1.

**DRUGS IN THE BLOOD PRESSURE REGULATION IN SEPTIC PATIENTS**

**Antibiotic therapy**

A type of bacteria and it’s treatment is important for both BP and survival in the sepsis and septic shock. A study of Kumar in the cohort of 2,154 septic shock patients confirmed a strong relationship between the delay in antimicrobial therapy after the onset of recurrent or persistent hypotension and in-hospital mortality (24). An early administration of an antimicrobial effective for causative pathogens within the first hour of registered hypotension (a MAP of <65 mm Hg) was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial treatment over the ensuing 6 hrs was associated with a mean decrease in survival of 7.6%. In multivariate analysis time to initiation of effective antimicrobial therapy was the single strongest predictor of the restoration of blood pressure and outcome (25).

Kumar have reported an observation that only 50% of septic patients received effective antimicrobial therapy within 6 hrs of documented hypotension (24, 25). Since infections can be confirmed in almost 80% of cases, predominantly originating from respiratory system (almost entirely pneumonia) and gastrointestinal or intra-abdominal sites

<table>
<thead>
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<th>Table 1. Age adjusted perfusion pressure and threshold pulse rates (Modified from: Carcillo JA, Fields AI; American College of Critical Care Medicine Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 2002; 30: 1365-1378.)</th>
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which together accounted for two thirds of all infections resulting in septic shock, this proportion is still unacceptably low. Therefore the special measures of infection identification, clinical examination and early antibiotic therapy with therapies aimed at blood pressure optimization may significantly improve outcome (8, 24).

Volume loading

Hypovolemia is the first imbalance targeted during the initial fluid resuscitation. New recommendations on the sepsis treatment proposed by International Surviving Sepsis Campaign Guidelines Committee (8) argue for the volume loading maintaining CVP at 8 mmHg, or 12 in the mechanically ventilated patients. A fluid challenge technique is preferred, starting with at least 1000 ml of crystalloids, or 300-500 ml of colloids over 30 min. Greater amounts of fluid and more rapid administration may be given in patients with sepsis induced tissue hypoperfusion. Fluid administration should be continued as long as the hemodynamic improvement continues, and reduced if CVP or pulmonary artery balloon-occluded pressure increases without concurrent hemodynamic and tissue perfusion improvement (8).

In the clinical praxis either natural/artificial colloids or crystalloids are used during the fluid resuscitation. Albumin solutions were proven as equally safe as crystalloids in the volume resuscitation, and hydroxyethyl starch (HES) infusions were beneficial in inducing haemodilution in the septic shock (8, 26). HES 130/0.4 infusion was as effective patients with sepsis as in controls without sepsis, and may remain within the intravascular space even in the septic patients (26). Since meta analyses have not confirmed the superiority of each solution in the volume resuscitation, current recommendations do not support the use of one type of fluid over another (8).

Vasopressors

Vasopressor therapy is required in the therapeutic management of hypotension in severe septic shock (8). Norepinephrine or dopamine are first choice vasopressor agents. Norepinephrine is often favoured because of its reliable effectiveness to achieve and maintain an adequate MAP, due to vasoconstrictive effects, with little change in heart rate and minor increase in stroke volume compared with dopamine (27).

Animal studies have confirmed that the use of norepinephrine was associated with improved MAP, sustained aortic and mesenteric blood flow, and better tissue oxygenation when compared with fluid resuscitation alone, irrespective of time of administration. Furthermore, the early use of norepinephrine with volume expansion was associated with a higher proportion of blood flow redistributed to the mesenteric area, lower lactate levels, and less infused volume (28).

Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (8). Although there are no high quality studies favouring one catecholamine over another, some of them have confirmed epinephrine’s potential for tachycardia and disadvantageous effects on splanchnic circulation and hyperlactemia. Epinephrine should be only used as an alternative drug in the septic shock patients poorly responsive to norepinephrine or dopamine (8).

Low doses of vasopressin may be effective in rising blood pressure in patients refractory to other vasopressors (8). Since vasopressin has quite a short half-time (6 mins), its analogue terlipressin, with a longer half-life (6 hrs), was investigated in numerous clinical trials (16, 29). The benefits and disadvantages of vasopressin or terlipressin over norepinephrine are still a matter of clinical investigations. In patients with hyperdynamic septic shock, both norepinephrine and terlipressin effectively raised mean arterial blood pressure, cerebral perfusion pressure and a urine production (14).

A major disadvantage observed with both pure vasoconstrictors is tissue ischemia. In such patients microcirculatory monitoring i.e. OPS imaging might provide a substrate for earlier ob-
servations of skin necrosis and a decline of gut mucosal circulation (14, 15).

The recent VASST trial comparing norepinephrine alone to norepinephrine plus vasopressin showed no difference in outcome between two groups of septic shock patients (30). SSC guidelines suggest that vasopressin 0.03 U min\(^{-1}\) may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (8).

**Inotropic therapy**

Dobutamine infusion (up to maximum of 20 \(\mu g\) kg\(^{-1}\) min\(^{-1}\)) is first line inotrope for patients with myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output (8). It should be used during the first 6 hrs of resuscitation of severe sepsis or septic shock, if hematocrit is \(\geq 30\%\) but SCVO\(_2\) of 70% or SvO\(_2\) 65% is not achieved with fluid resuscitation to the CVP target. In the septic patients who remain hypotensive after fluid resuscitation, a treatment with a combined inotrope/vasopressor such as norepinephrine or dopamine is recommended if cardiac output is not measured. When cardiac output in addition to blood pressure is monitored, a vasopressor such as norepinephrine may be administered separately to target desired levels of MAP and cardiac output (8).

Adequate fluid resuscitation is a fundamental therapy in patients with septic shock, and should ideally be achieved before vasopressors and inotropes are used. However, using vasopressors as an emergency measure in patients with severe shock is frequently necessary, even when hypovolemia has not yet been resolved (8, 24).

Vasopressors should be administered through a central venous catheter. Arterial line has to be placed as soon as possible to allow continuous analysis and reproducible measurement of AP. Using these catheters, decisions regarding therapy can be based on immediate and reproducible blood pressure information (8).

**Corticosteroids**

Corticosteroids were proposed for the treatment of sepsis as early as 1940. A rationale is an adrenal insufficiency which is present in about half of patients with septic shock and is associated with higher rates of refractory hypotension and mortality (31).

A moderate dose of glucocorticoids appears to be beneficial in the patients with relative adrenal insufficiency (nonresponders to the corticotropin test) (32).

Intravenous corticosteroids are currently recommended only for hypotensive adult septic shock patients who are poorly responsive to adequate fluid resuscitation and vasopressors. In such patients high doses of corticosteroids are not beneficial. A replacement dose of hydrocortisone, about 300 mg daily for 5-7 days, should be used instead of it (31). Hydrocortisone is preferred to dexamethasone in the treatment of septic shock, although it was not confirmed as effective in all patients. In the patients with hydrocortisone hastened reversal of shock it increases arterial pressure and improves 28-day mortality (33). A meta-analysis of all available clinical controlled studies showed a reduction in 28 days and in-hospital all-cause mortality with glucocorticoids (31, 33).

**Other supportive therapies in the sepsis**

Blood products should be given to target hemoglobin of 70.0–90.0 g L\(^{-1}\), or \(\geq 100\) in patients with myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease or lactic acidosis (8, 27).

A bicarbonate therapy is not recommended for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH \(\geq 7.15\) or high blood lactate concentration (8).

To counterbalance activated coagulation cascade in the septic patients, several haemostatic agents (ATIII, TFPI, heparin) were investigated by means of improving outcome (8). Among
them only a recombinant version of activated protein C (rhAPC) is currently recommended in the sepsis treatment. The rhAPC treatment should be considered in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or MOF) if there are no contraindications (8). De Backer and colleagues have used an OPS imaging technique and confirmed that proportion of perfused capillaries increased in the rhAPC treated patients with a more rapid resolution of hyperlactatemia already at 4 hrs (from 64% to 84%, p < .01) but not in the control group treated using standard treatment (13).

Other therapies, including bacterial modulators (antiendotoxin, lipopoysacharide-binding protein [LPB], antiCD14 monoclonal antibody), anti-cytokines (IL-1ra, anti-TNF, sTNF-r, TNFR:Fc), antiinflammatory agents (leukocyte adhesion molecule inhibitors), iNOS inhibition, antioxidants, thromboxane antagonists, bradykinin receptor antagonists are now investigated in the population of patients with severe sepsis (34, 35). The treatment of sepsis in the immunocompromised patients represents a special problem. It is very often unsuccessful and with lethal outcome (25).

REVERSIBILITY OF CIRCULATION CHANGES IN THE SEPTIC PATIENTS

A reversibility of hemodynamic changes in the sepsis correlates with several parameters: the type of underlying bacteria, timing of antimicrobial agents and with the reactivity to catecholamine stress. A dynamic cardiovascular response to catecholamines is well recognized marker of mortality in septic patients (19). Kumar identified two critical parameters highly correlating with survival: catecholamine induced increase in the stroke volume and preserved cardiovascular reserve including preload reserve (19).

The endpoints of vasopressor therapy and other supportive therapies are adequate BP, normalization of the heart rate, regional and global perfusion with capillary refill of < 2 seconds, warm extremities with no differences between peripheral and central pulses, normal blood lactate concentrations, urine output > 1mL kg⁻¹ hr⁻¹, and normal mental status (8). Reversal of septic shock was defined as the maintenance of a systolic blood pressure of at least 90 mm Hg without vasopressor support for at least 24 hours (33).

The blood pressure deregulation with profound hypotension is a life threatening complication in the severe sepsis and septic shock. An identification and early therapy of this life threatening disorder may significantly improve outcome.

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Written consent was obtained from the child’s parents for publication of the Figure 1.

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