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Early Hemodynamic Management of Critically Ill Burn Patients

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BURN injury is associated with early profound hypovolemia followed by a systemic inflammatory response with a subsequent hyperdynamic state.[1] Hemodynamic management has long been identified as a key factor impacting burn patients' prognosis.[2] Because both under- and over-resuscitation may potentially negatively impact outcome, anesthesiologists and intensivists caring for burn patients will have to face the challenge of fluid balance in these patients.[3,4] The aim of this review is to provide an overview of the hemodynamic consequences of burn injury and to propose strategies for the initial hemodynamic management of severe burn patients using the available evidence-based medicine combined with a physiologic approach.

Cardiovascular Consequences of Burn Injury

Burn Edema Process

Severe burn injury leads to tissue destruction with capillary leak. Edema starts within the first hour after injury in burned tissues. Thereafter, a slower increase in fluid extravasation in both injured and noninjured tissues occurs during the first 24 to 48 h after burn injury when systemic inflammatory response occurs.[5]

The pathogenesis of burn edema involves all the physical forces described by the conventional Starling law. Fluid movement into the interstitium results from the combination of an imbalance between hydrostatic and oncotic forces, together with increase of vascular permeability. The development of gaps in endothelial cell junction with an increase in capillary permeability favors fluid and protein loss into the interstitium in burn tissue and only fluid in the nonburned tissue (fig. 1).[5]

Capillary filtration and reabsorption are also strongly affected by the integrity of the glycocalyx.[6] The endothelial glycocalyx is a dynamic structure composed of cell-bound proteoglycans and sialoproteins (1 to 3 μm in thickness) that envelop endothelial cells on their luminal side and inside the endothelial paracellular clefts. It plays a central role in vascular permeability (mainly paracellular permeability) by maintaining the oncotic gradient across the endothelial barrier. Accordingly, the oncotic gradient between the plasma and interstitial spaces is set between plasma and glycocalyx (subglycocalyx oncotic pressure) rather than being transendothelial as described in the traditional Starling model.[7] Inflammatory injury (sepsis, trauma, thermal injury) to the glycocalyx increases paracellular permeability, which is associated with fluid and albumin leak into the interstitial space (fig. 1).[6]

Urinary microalbuminuria was described as a marker of systemic endothelial permeability.[8] In an experimental model of sepsis, albumin leakage into urine increased in association with glomerular barrier glycocalyx alteration.[9] Syndecan-1 and endocan have been proposed as other biomarkers of glycocalyx degradation and endothelial injury in septic and trauma patients.[10] In a recent study using syndecan-1 as a surrogate marker of glycocalyx shedding in a population of burn patients, Osuka *et al.* found that after adjustment for age, sex, percent total body surface area, and inhalation injury, syndecan-1 was an independent marker of the increase in fluid requirements ($P = 0.04$).[11]

Hemodynamic Patterns of Burn Shock

Burn injury leads to initial systemic and pulmonary vasoconstriction, (related to catecholaminergic release and hemolysis), low cardiac output (CO), and low oxygen delivery and

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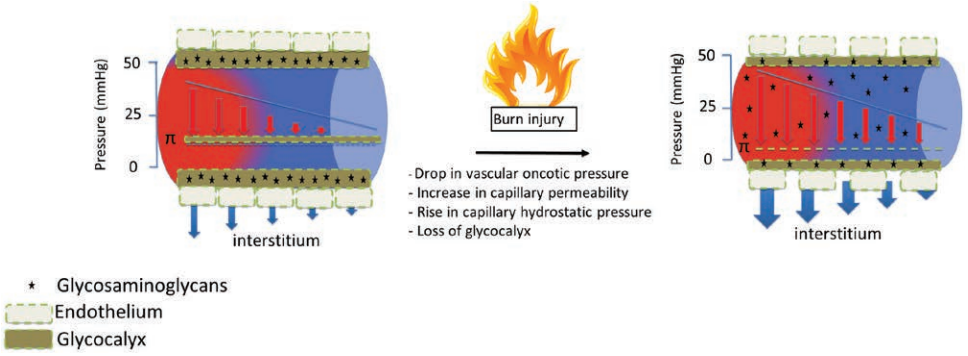

Fig. 1. Pathophysiology of capillary leak syndrome in critically ill burns. Fluid accumulation into the interstitium results from the combination of an imbalance between hydrostatic and oncotic forces favoring the fluid movement into the interstitium together with increase of vascular permeability and glycocalyx degradation. *Red arrows* indicate intravascular hydrostatic pressure, *blue arrows* indicate oncotic pressure, and *green broken lines* indicate glycocalyx. Π = Oncotic pressure.

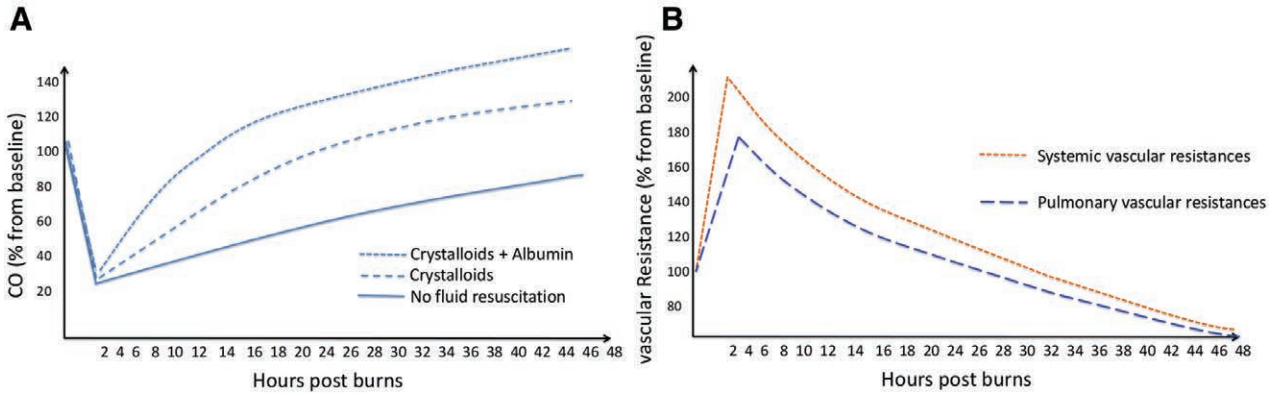

Fig. 2. Burn shock hemodynamic pattern in the first 48 h. In the first hours, burn injury leads to initial low cardiac output (CO; *A*) and systemic and pulmonary vasoconstriction (*B*). Within 24 to 48 h, a hyperdynamic and vasoplegic state develops, which is characterized by a high CO (*A*) and decreased systemic and pulmonary vascular resistances (*B*). This pattern was observed with or without fluid resuscitation. Fluid resuscitation was, however, associated with a faster restoration of CO as well as higher CO during the hyperdynamic phase, especially when albumin is infused with crystalloids. Figure adapted from Asch *et al.*[1]

consumption.[1] Within 24 to 48 h, a hyperdynamic and vasoplegic state develops, which is characterized by a high CO, increased oxygen consumption, and decreased systemic vascular resistance.[12,13] Interestingly, this pattern was observed with or without fluid resuscitation in animals. Fluid resuscitation was, however, associated with a faster restoration of CO as well as a higher CO during the hyperdynamic phase (fig. 2).[1]

Burn-associated Cardiac Injury

Severe thermal injury can also induce cardiac dysfunction with impaired left ventricular systolic function, slowed isovolemic relaxation, and decreased diastolic compliance.[14] Cardiac stress can result in left heart failure and increased left cardiac filling pressures, which may further promote extravascular fluid transfer into the lungs. An increase in right ventricular workload may also lead to right heart failure, increase in right ventricular filling pressure, and venous congestion.[15]

Microcirculatory Alterations

Alterations of microcirculatory blood flow can further compromise organ perfusion. These microcirculatory derangements were described mainly in the splanchnic territory and the skin (in both injured and noninjured tissues) using gastric tonometry and skin laser Doppler and microdialysis, respectively.[16,17] Microcirculatory derangements were associated with organ failure and poor outcome.[13] The development of tissue edema with fluid resuscitation may lead to venous occlusion and increased vascular resistance as well as disseminated intravascular coagulation in the microvasculature and altered erythrocyte deformability.[18] Furthermore, burn-related hemolysis and the use of hydroxocobalamin after inhalation injury may lead to vasoconstriction and compromise the microperfusion through vasoconstriction due to the scavenging effect of nitric oxide.[19,20]

Risks of Fluid Under- and Over-resuscitation in Burn Patients

The main challenge in the initial fluid administration strategy is to avoid significant hypovolemia, which may induce hypoperfusion, but without over-resuscitating the patient. Under-resuscitation may lead to acute kidney injury and nonocclusive mesenteric ischemia.[3,21] On the other hand,

the risk of abdominal compartmental syndrome, acute kidney injury, and acute respiratory distress syndrome (ARDS) are the most easily identified consequences of fluid overresuscitation.[4,22] Abdominal compartmental syndrome and ARDS result from the combination of large fluid resuscitation volumes and systemic capillary leak syndrome. In a pediatric study, patients who received large volumes of fluid resuscitation represented an at-risk group for respiratory failure after a scald injury (7.66 *vs.* 4.07 ml/kg per percent total body surface area, $P < 0.001$).[23] Another study confirmed that higher crude rates of ARDS were observed in patients who received standard or excessive resuscitation (greater than 4 ml/kg per percent total body surface area) than those patients who received restricted resuscitation.[4] Furthermore, the association between a large positive fluid balance and the onset of acute kidney injury was reported in severe burns and suggests a role of venous congestion in the development of acute kidney injury.[24] Interestingly, hypervolemia promotes fluid extravasation into the interstitial space. A rapid rise in intravascular hydrostatic pressure will increase the hydrostatic gradient pressure and therefore increase transcapillary fluid extravasation according to the Starling forces. A decrease in intravascular oncotic pressure due to hemodilution after crystalloids infusion will further promote extravascular fluid leakage. Finally, hypervolemia has been shown to alter the glycocalyx and therefore increase vascular permeability.[11,25] Therefore, except for critical hypovolemic hypotension, rapid large-volume fluid boluses might be undesirable in order to limit these three factors promoting extravascular fluid leakage (fig. 3).

Hemodynamic Targets in Early Resuscitation of Critically Ill Burn Patients

The Parkland formula is most commonly used to predict the required fluid volumes. Although the Parkland formula

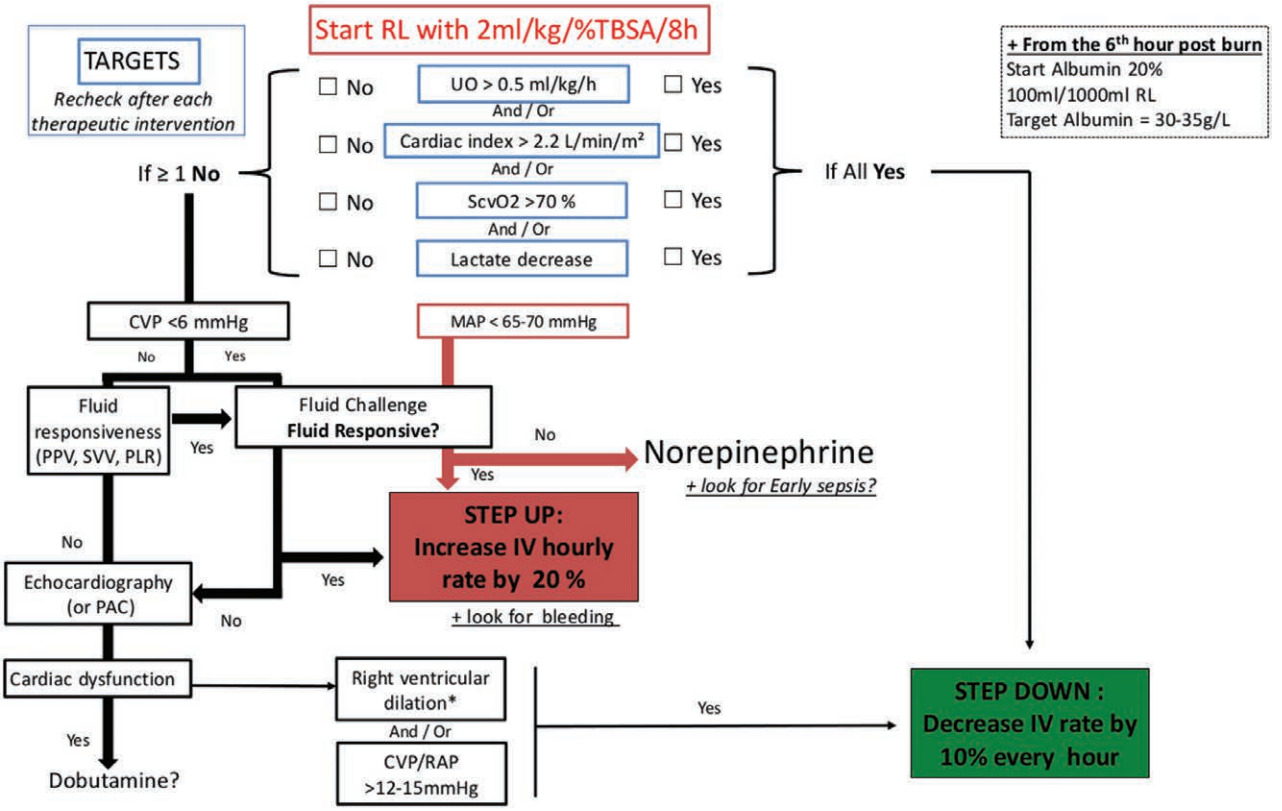

Fig. 3. Saint Louis Hospital hemodynamic management algorithm. Cardiac output, invasive arterial pressure, and central venous pressure (CVP) are monitored in patients with greater than 30% total body surface area burned (TBSA), or greater than 20% TBSA in patients with comorbidities, or severe smoke inhalation injury or patients with hemodynamic instability. Start resuscitation with 2 ml · kg^{-1} · %TBSA^{-1} · 8h^{-1} of crystalloids with four main goals (urinary output [UO] greater than 0.5 ml · kg^{-1} · h^{-1}, cardiac index greater than 2.2 l · min^{-1} · m^{-2}, central venous oximetry [$ScvO_2$] greater than 70%, lactate decrease). If one of these targets is not reached with CVP less than 6 mmHg or positive dynamic tests (passive leg raising [PLR], pulse pressure variation [PPV], stroke volume variation [SVV]) or mean arterial pressure (MAP) less than 65 to 70 mmHg, test fluid responsiveness or perform a fluid challenge. If the patient is not a fluid responder, then introduce norepinephrine, perform an echocardiography, and search for a cardiac dysfunction. If the patient is a fluid responder, then step up and increase IV crystalloids rate by 20% and then recheck each target hourly. If all targets are reached, then step down IV crystalloids rate by 10% every hour and recheck each target hourly. *If the patient has acute respiratory distress syndrome, use inhaled nitric oxide? Perform prone position? PAC = pulmonary artery catheter; RAP = right atrial pressure; RL = Ringer's Lactate.

has long been considered as the reference, it remains rough and inaccurate for several reasons. First, there are obvious interindividual variations between fluid requirements due to different host responses to burn injury and/or smoke inhalation injuries and extreme ages and comorbidities. Many factors other than percent total body surface area burn and body weight may influence fluid requirements in severely burned patients: burn depth, burn mechanism, associated trauma, early escharotomy or fasciotomy, and inhalation injury. Higher fluid requirements may result from the intensive inflammatory response with capillary leak after inhalation injury. Finally, estimating the body weight and the burn total body surface area can be challenging, and errors in such evaluation can lead to errors in the fluid requirements estimation.

Of note, using the Parkland formula, half of the volume should be given within 8 h of the burn injury and half during the next 16 h. This only approximates the fluid needs during the very first hours. This approach also overlooks the dynamic nature of the circulation during the first 24 h (fig. 2). In a study including critically ill burn patients, stroke volume and cardiac index within the first hour after admission were independently associated with 90-day mortality regardless of total body surface area.[26] For these reasons, we strongly recommend hourly assessment of hemodynamics during the first 24 h of burn shock with hourly adjustment of fluid needs (fig. 3). Fluid volume requirements are routinely based on mean arterial pressure and urine output. However, these physiologic targets have been recognized as poor resuscitation endpoints, not accurately reflecting CO or the adequacy of oxygen delivery.[27] A decrease in urine output may be associated with a prerenal cause (*e.g.*, a decrease in renal blood flow or renal perfusion pressure due to fluid depletion), but other causes of acute kidney injury in burn patients include hemolysis, rhabdomyolysis, inflammation and immune-related response, and intrarenal vasoconstriction due to neurohormonal activation, which may lead to an uncoupling between intravascular volume and urine output. In contrast, venous congestion related to an increased venous pressure due to increased cardiac filling pressure and/or increased abdominal pressure can lead to oliguria. In these settings, fluid loading would obviously not represent the right response to low urine output. On the other hand, an increase in urine output and glomerular filtration rate may be observed after a rapid drop in plasma albumin concentration, increasing the glomerular transcapillary fluid rate fraction or hyperglycemia-related hyperosmolarity.[28] In a retrospective study, variations in urine output and vital signs were poorly correlated with oxygen parameter changes (oxygen delivery and consumption) after fluid loading.[27] Sánchez *et al.*, in a prospective cohort study, reported that oliguric patients did not show differences in cardiac index, intrathoracic blood volume, or lactate concentrations compared to nonoligurics.[29] To summarize, low urine output (*e.g.*, less than 0.5 ml · kg^{-1} · h^{-1}) represents an alarm sign that should prompt rapid investigation of the hemodynamic status. However, urine output *per se* cannot be considered as a reliable parameter of hypovolemia.[30]

Goal-directed Resuscitation Therapy

Goal-directed fluid resuscitation therapy based on more advanced hemodynamic monitoring to reach alternative targets has been suggested to better tailor fluid resuscitation.[31,32] Serum lactate and base deficit have been found to be associated with outcomes in major burns, and proposed as endpoints of initial resuscitation.[29,33] Low CO and oxygen delivery were also associated with poor outcome in critically ill burn patients.[13,26]

Only a few randomized controlled trials have compared fluid resuscitation based on the Parkland formula with a goal-directed therapy strategy. Csontos *et al.* compared the effect of two resuscitation regimens (based on urine output *vs.* intrathoracic blood volume) on the multiple organ dysfunction syndrome and central venous oximetry in the first 72 h.[34] The mean central venous oximetry was significantly lower in the urine output group than in the intrathoracic blood volume group (68% [64 to 71] and 74% [71 to 78], respectively; $P = 0.024$) for the first 24 h. The multiple organ dysfunction syndrome score was significantly higher in the urine output group than in the intrathoracic blood volume group at 48 h (5 [4.3 to 5.8] *vs.* 4 [3 to 4.3], respectively; $P = 0.024$) and 72 h after injury (5 [4.3 to 6] *vs.* 3 [3.3 to 3.8], respectively; $P = 0.014$) without any impact on mortality.

In a randomized controlled trial using continuous real-time CO monitoring with arterial pulse counter analysis and an algorithm testing fluid responsiveness with dynamic preload parameters, crystalloid volume administration was found to be lower than in the control group (5,090 ± 680 ml *vs.* 7,820 ± 1,050 ml, $P = 0.04$) while no difference was found in relation to organ dysfunction and mortality.[35] Arlati *et al.* observed that fluid administration guided by a hemodynamics-oriented approach in the first 24-h period limited to a urine output of 0.5 to 1 ml · kg^{-1} · h^{-1} and a cardiac index of at least 2.2 l · min^{-1} · m^{-2} was safe, resulting in lower fluid volume administration and less organ dysfunction.[2] In a retrospective case series including burn patients, a goal-directed therapy strategy was associated with better outcome than conventional management.[32] In a systematic review and meta-analysis including 20 studies, a decrease in mortality was found with the use of certain hemodynamic alternative endpoints (mainly cardiac index and intrathoracic blood volume) rather than hourly urine output (risk ratio, 0.77; 95% CI, 0.42 to 0.85; $P < 0.004$).[31]

In contrast, studies that have used a fluid resuscitation strategy mainly based on normalization of static preload parameters (intrathoracic blood volume greater than 800 ml/m^2) found a significant increase in fluid administration in comparison with using the Parkland formula. In a study including 50 patients with a total body surface area greater than

20%, Holm *et al.* compared the results of fluid administration strategy according to the Parkland formula *versus* a goal-directed therapy based on intrathoracic blood volume as an endpoint. Fluid volume administration was higher in the intrathoracic blood volume group compared to the Parkland group without a significant difference in CO and outcome.[36] In a randomized controlled trial by Aboelatta and Abdelsalam, fluid administration in the initial 72 h after thermal injury was significantly higher in the intrathoracic blood volume group.[37]

To summarize, it appears that fluid resuscitation targeting static preload parameters (intrathoracic blood volume, central venous pressure [CVP]) would lead to over-resuscitation without outcome benefit. The goal of hemodynamic monitoring is to ensure adequate oxygen delivery, ensuring a minimum CO in the absence of poor perfusion. An algorithm based on these observations is proposed in figure 3. Parameters of potential inappropriate organs perfusion (*e.g.*, low urine output, mean arterial pressure and CO, high lactate plasma concentration) should lead to evaluation of fluid responsiveness. The use of dynamic parameters should be preferred (absolute value of pulse pressure variation and stroke volume variation, intraindividual changes in pulse pressure variation, passive leg raising). Static preload parameters (*e.g.*, intrathoracic blood volume, CVP) should not be viewed as hemodynamic targets but as safety parameters (*e.g.*, CVP upper limit of 12 to 15 mmHg). In fluid unresponsive patients with cardiovascular or renal failure, other mechanisms of shock should be considered and lead to assessment of cardiac function.

Types of Fluids

Crystalloids Solutions

Ringer's Lactate (Baxter Healthcare, USA) is the most used crystalloid in burns. Emerging evidence suggests that the administration of chloride-rich solutions (*e.g.*, sodium chloride 0.9%) in critically ill patients is associated with a higher incidence of hyperchloremic acidosis and acute kidney injury.[38] Given the large volumes employed during burn shock resuscitation, the use of balanced solutions as first-line solutions is preferred in severe burn patients. A randomized controlled trial comparing two balanced solutions (Plasmalyte [Baxter Healthcare, Australia] *vs.* Ringer's Lactate) in major burns is ongoing (ClinicalTrials.gov identifier: NCT03118362).

Colloids Solutions

The use of colloids in the first 24 h of burn resuscitation is controversial since the capillary leak may cause a transcapillary passage of large molecules into the interstitial space. Nevertheless, the onset of burn-related endothelial dysfunction and capillary leak was shown to be within 2 h after thermal injury with a median duration of 5 h.[39] Human albumin has multiple physiologic effects, including regulation of colloid osmotic pressure, antioxidant properties, nitric oxide modulation and buffer capabilities, plasmatic binding, and transportation of various substances, which may be of particular relevance in severe burn injury.[40]

In a recent meta-analysis, use of albumin in the first 24 h was not associated with increased survival in severely burned patients. Nonetheless, significant statistical heterogeneity was present, and after exclusion of two studies at high risk of bias, albumin infusion was associated with reduced mortality (odds ratio [95% CI], 0.34 [0.19 to 0.58]; $P < 0.001$) and with decreased occurrence of compartment syndrome (pooled odds ratio [95% CI], 0.19 [0.07 to 0.50]; $P < 0.001$).[41] In a multicenter unblinded controlled trial in burn patients with total body surface area greater than 20%, Cooper *et al.* observed no significant difference between the treatment (5% albumin) and control groups (Ringer's Lactate) in organ failures.[42] In a before-after study, Park *et al.* observed that the use of 5% albumin in the first 24 h (*vs.* Ringer's Lactate and a synthetic colloid) was associated with lower mortality, use of vasopressors, duration of mechanical ventilation, and ventilator-associated pneumonia incidence.[43] Lawrence *et al.* performed a retrospective observational study where they observed that 5% albumin administration was associated with a reduction in crystalloid requirements.[44]

The current available evidence suggests that exogenous albumin administration in the first 24 h of burn shock resuscitation might be associated with better outcomes.[40] However, the optimal timing, dose, concentration, targeted albumin concentration, and patient population for albumin use remain unclear. Adequately powered, multicenter randomized controlled trials should be undertaken in burn patients.

The European Medicines Agency (London, United Kingdom) contraindicated the use of hydroxyethyl starch in burn patients. This decision was mainly based on the results of studies and meta-analyses, carried out mainly in populations of nonburn patients, showing that the use of these solutions was associated with a higher incidence of mortality and acute kidney injury.[45]

Catecholamine Use in Early Burn Shock

Data regarding vasopressor use in the early phase of burn shock are scarce. In our experience, vasopressors are usually necessary in the hyperkinetic and vasoplegic phase (sepsis-like phase). Norepinephrine can increase stressed blood volume, venous return, and CO and may therefore limit the amount of administered fluids. Indeed, in hemodynamic physiology, vascular volume has two components. One part simply fills vessels but does not stretch the walls, and is called unstressed volume. The other part stretches the elastic walls and accounts for venous pressure and is called stressed volume. Only stressed volume determines venous return. Sufficient intravascular volume without very profound hypovolemia, however, is needed to allow recruitment of stressed volume.

Adjunctive Therapies

Major thermal injury causes an important inflammation and production of free oxygen radicals. Antioxidants have been proposed as adjunctive therapies to initial resuscitation. In a randomized controlled trial, adjuvant administration of high-dose ascorbic acid ($66\,mg \cdot kg^{-1} \cdot h^{-1}$) during the first 24 h after burn injury significantly reduces fluid volume requirements (5.5 *vs.* 3.0 ml/kg per percent total body surface area, $P < 0.01$).[46]

Furthermore, low-dose hydrocortisone could reduce shock duration in vasopressor-dependent severely burned patients, possibly by a reduction in capillary leakage and a correction of adrenal insufficiency. In a randomized controlled trial, median norepinephrine treatment duration was shorter in the corticosteroid-treated *versus* the placebo group (57 *vs.* 120 h, $P = 0.035$) without a difference in mortality.[47] Nevertheless, the impact of hydrocortisone administration remains controversial with respect to the immune system and the risk of secondary infection in burn patients.

Conclusions

Initial hemodynamic resuscitation of critically ill burn patients is a challenge with the dual purpose of avoiding under- and over-resuscitation. Balanced crystalloids solutions together with albumin represent the cornerstone of the resuscitation strategy, which we believe should be guided by hemodynamic monitoring. There are, however, many knowledge gaps regarding the hemodynamic targets, role of colloids, adjuvant therapies, vasopressors, and their impact on outcome and the immune system that should be addressed in the near future (see table with research agenda, Supplemental Digital Content, http://links.lww.com/ALN/B737).

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Competing Interests

Dr. Legrand discloses consulting income from Sphingotec (Hennigsdorf, Germany), Novartis (Basel, Switzerland), and Baxter Healthcare (Deerfield, Illinois). The other authors declare no competing interests.

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