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Selection of Target Mean Arterial Pressure in Severely Burned Patients with Septic Shock

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Summary

The timely diagnosis of both sepsis and septic shock can be challenging in severely burned patients. Monitoring methods providing early diagnosis of organ dysfunction development are of great importance. Assessment of the glomerular filtration rate with central hemodynamic parameters can be considered as a component of comprehensive monitoring of effectiveness of septic shock therapy.

Aim: to determine the relationship between the target mean arterial pressure and glomerular filtration rate parameters in the treatment of severely burned patients with septic shock.

Material and methods. 158 severely burned patients with septic shock were included in the study, of them 121 patients represented a retrospective historical group, and 37 patients constituted a prospective group. The main criteria of treatment efficacy were28-day and hospital mortality.

Results. In the patients of prospective group, 28-days mortality decreased down to 16.2% compared with 33.9% in the retrospective group, and hospital mortality dropped down to 29.7% vs 42.1%, respectively (P<0.05).

Conclusion. Extended hemodynamic and metabolic (renal function assessment) monitoring of intensive therapy of severely burned patients with septic shock helps targeted adjustment of fluid therapy and provides earlier beginning of extracorporeal blood therapy thus favoring better survival rate.

Keywords: sepsis; septic shock; burns; central hemodynamics; hemodynamic monitoring; fluid therapy; vasopressors

Conflict of interest. The authors declare no conflict of interest.

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Introduction

According to the current classification, septic shock is characterized by circulatory failure manifesting as hypotension and increased lactate level of more than 2 mmol/L (despite adequate fluid therapy), and requiring vasopressors to maintain mean arterial pressure greater than 65 mmHg [1]. Intensive care strategy proposed by Rivers E. et al. [2] aimed at optimizing oxygen delivery (increasing cardiac performance, oxygenation and hemoglobin concentration depending on clinical setting), with clear goals and monitoring algorithm, has contributed to a significant reduction of mortality, which was 44.3% versus 56.9% with the conventional approach. At the same time, several studies have shown that the baseline parameters of myocardial contractile function were not impaired (systolic dysfunction was observed in only 20% of patients), while the patients with diastolic dysfunction (50%) responded negatively to fluid therapy [3–7]. In such cases, any volume of IV fluid may be redundant, and infusion therapy strategy could be regarded as aggressive and provoking progression of diastolic dysfunction [8]. However, the impact of increased venous pressure on renal function by reducing renal blood flow and glomerular filtration rate has been noted, which certainly directly or indirectly worsens organ dysfunction [9, 10]. In the concept of «three hits» of septic shock (C. Cordemans, 2012) [11] only during the «first hit» stage, when hypotension, hypovolemia, and oliguria develop, the control of mean arterial pressure, central venous blood saturation, urine output and lactate level can effectively ensure patient safety, reflecting the treatment efficacy.

For severely burned patients, the issue of diagnosing both sepsis and septic shock is even more relevant than in other patient groups [12]. In the early phase of burn injury, the patient's clinical status may correspond to the «second hit» of septic shock, which is related both directly to the mechanism and severity of the injury and to the hyperhydration syndrome due to excessive fluid infusion. Moreover, early burn sepsis/septic shock is characterized by an extremely severe and often fulminant course with a high risk of death [13, 14]. Monitoring methods enabling accurate and specific diagnosis of the causes of organ perfusion disturbances will be of particular importance. Despite all its limitations, the measurement of systemic arterial pressure remains an integral component of current comprehensive hemodynamic monitoring because all other elements characterizing abnormal parameters and their contribution to the development of central hemodynamic disturbances, are based on the systemic arterial pressure measurement. The latest concepts of shock therapy, including the four-phase model of fluid therapy in shock (ROS-D/ROSE concept which implies rescue, optimization, stabilization, de-escalation), suggesting a phase-based approach to hemodynamic control with sequential use of hemodynamic monitoring by echocardiography, blood flow ultrasound scan, continuous measurement of blood lactate and central venous blood saturation, as well as specific volumetric parameters, are still initially based on the measurement of blood pressure [15–17]. The prerequisites for personalization of acceptable levels of systemic blood pressure in different groups of patients have been introduced, for example, in patients with septic shock and baseline hypertension, the maintenance of higher blood pressure values is recommended [18]. Glomerular filtration rate (GFR) less than 60 mL/min/m^2 has been found to increase the risk of death from cardiovascular failure by several times compared to values between 75 and 60 mL/min/m^2 [17, 19, 20]. Adding GFR monitoring for evaluation of the efficacy of septic shock therapy helps develop a tailored approach to choosing optimal hemodynamic parameters [21, 22].

The aim of our study was to determine the relationship between target mean arterial pressure and glomerular filtration rate parameters during the treatment of severely burned patients with septic shock.

Material and Methods

A single-center screening study was performed in 328 patients with burn injury hospitalized in the Burn Unit of the Vishnevsky Research Medical Center of Surgery in 2011–2021, including a retrospective analysis of medical records of 277 patients during 2011–2017 and a prospective study in 51 patients during 2018–2021. The inclusion criteria were septic shock (diagnosed according to Russian Association of Surgical Infection Specialists (RASIS) (2004) and SSC (2008) guidelines in the retrospective 2012–2016 group and RASIS 2016 and «Sepsis 3» in the prospective group) [1, 23–26]; hemodynamic monitoring data; lactate levels; urine output; daily urine biochemical study parameters; biomarkers of systemic infection; specific treatment information and its efficacy assessment. Exclusion criteria were age <18 years; lack of the above data; arterial hypotension during fluid therapy and use of catecholamines at the time of screening. In accordance with the stated criteria, 158 patients (121 in the retrospective and 37 in the prospective groups) were included in the study.

During the analysis, a subgroup of patients with baseline hypertension (AH subgroup) was identified. At the time of inclusion, they significantly differed from the other normotensive patients in age (60.3 vs 57.0 years, respectively).

The patients in the prospective group were divided into three subgroups with vasoplegic (n=30), vasoplegic-hypovolemic (n=4), and cardiomyopathic type (n=2) hemodynamics based on hemodynamic monitoring data and the results of retrospective study.

Most patients (151 [95.6%]), suffered from flame burn injury with involvement of over 30% of body surface area. Seven (4.4%) patients had electrical injury in combination with electric arc-related skin thermal injuries. Inhalation burn injury was diagnosed in 38 (24.1%) patients. The overall severity of patients' condition when transferred to the intensive care unit was assessed using SAPS 3 severity and prognosis scale [27, 28]. The lethal outcome prognosis reached 73.55 (±11.2) in the retrospective group and 74.6 (±5.8) in the prospective group (Table).

Due to the different times of data collection and arrangement and the use of various sepsis treatment guidelines, the group homogeneity was not considered mandatory for comparative analyses. The results of treatment were assessed using universal criteria based on the mortality rate.

In most cases (76.9% of patients), the septic shock was associated with a wound infection. Pulmonary sepsis occurred in 23.1% of cases. Infectious nature of the complications was determined by typical clinical signs characteristic of the systemic inflammatory response. In addition, there was evidence of a significant increase in the levels of systemic infection biomarkers such as procalcitonin and C-reactive protein (Table).

All patients received intensive treatment according to the current international and national guidelines of professional medical societies on treatment of septic shock and organ dysfunction management including mechanical lung ventilation, fluid therapy, vasopressor support, and anticoagulants. Antimicrobial drugs were prescribed based on the baseline epidemiological data empirically or in a targeted manner when infection was confirmed by positive microbiological tests of tissue biopsy specimens, airway secretions, or blood.

Comprehensive invasive monitoring using PiCCO technology (Pulsion Medical Systems, Munich, Germany) was performed with the measurement of cardiac index (CI), global end-diastolic volume (GEDV), extravascular lung water index (EVLWI), and total peripheral vascular resistance (TPVR). Hemodynamic profile changes with thermodilution

General characteristics of patients and baseline criteria of infection.

Parameters	Parameters values in groups	
	Retrospective group (*n*=121)	Prospective group (*n*=37)
Sex (male/female), *n*	69/52	18/19
Age, years	58±15.7	51±11.3
Frank's index of burn severity, Units (min–max)	94 (83–188)	91 (76–179)
Soft tissue skin injury, *n*	93	36
Chest organ injury, *n*	28	1
CHF, NYHA II–III, *n* (%)	6 (4.9)	8 (21.6)
Respiratory failure grade II–III, *n* (%)	4 (3.3)	1 (2.7)
Hypertension, *n* (%)	43 (35.5)	8 (21.6)
Insulin dependent diabetes mellitus, *n* (%)	16 (13.2)	3 (8.1)
Obesity, *n* (%)	13 (10.7)	8 (21.6)
SOFA scale (points)	8.5±1.9	9.3±0.7
SAPS 3 scale, %	73.55 (±11.2)	74.6 (±5.8)
Heart rate, bpm	112.4 (94; 143) SD 17.5	116.5 (42; 139) SD 13.1
Body temperature, °C	38.4 (35.4; 38.9) SD 2.3	38.6 (35.1; 39.4) SD 1.4
PCT, ng/ml	14.2 (2.4; 97.4) SD 17.1	13.2 (1.7; 43.2) SD 12.1
CRP, mg/l	256.5 (53.6; 413) SD 62.4	356.5 (43.2; 489) SD 41.4
WBC count, $\times 10^9$/l	17.2 (2.7; 49.6) SD 8.3	24.2 (3.2; 39.7) SD 6.4
Neutrophils, %	25.3 (13; 43) SD 8.3	23.6 (9.7; 42.8) SD 7.2

Note. CHF — chronic heart failure; NYHA — New York Heart Association; SOFA — Sequential Organ Failure Assessment; SAPS — Simplified Acute Physiology Score; PCT — procalcitonin; CRP — C-reactive protein. The data of the last 6 rows are presented as *M* (min; max).

curves were recorded every 8 hours over 72 hours of treatment. Hemodynamic disturbances and methods of their correction were interpreted according to the guidelines of the Department of Anesthesiology and Resuscitation, Northern State Medical University [29].

We assessed central venous blood saturation ($ScvO_2$), lactate level, and glomerular filtration rate (GFR) every 4 hours from the start of monitoring and primary assessment of circulatory disturbance type. Continuous control of respiratory mechanics and gas exchange was performed using the capacities of the ventilator and gas analysis module of the monitoring system. Parameters of myocardial electrophysiology, heart rhythm and pulse oximetry were also recorded through the monitoring complex. Biochemical urine investigation (every 24 hours after connection to the monitoring system) was performed to determine nitrogen balance and control natriuresis due to a high risk of hypernatremia and hyperosmolar syndrome in severely burned patients, as well as to control hypermetabolism. Glomerular filtration rate (GFR) was calculated retrospectively on the basis of endogenous creatinine clearance measurement data using the results of biochemical study of daily urine by Rehberg–Tareyev method [30, 31].

The conclusion about hemodynamic stabilization was made based on the achievement of mean arterial pressure (MAP), sufficient to maintain glomerular filtration rate over 60 ml/min/m^2. If this value was not achieved at 12–24 hours of follow-up (regardless of the corresponding hemodynamic parameters), patients were started on renal replacement therapy with prolonged veno-venous hemo(dia)filtration (20–35 ml/kg/hr). The main clinical and laboratory parameters in the prospective group were recorded in correlation with the stages of data acquisition in the retrospective stage. The 28-day and hospital mortality rates were chosen as the main efficacy criteria when comparing treatment regimens in the retrospective and prospective stages.

Microsoft Access database was used to store the data obtained. Statistical analysis was performed using the STATISTICA 6.0 software package (StatSoft, USA). The data distribution was assessed using the Kolmogorov–Smirnov test. In the case of normal distribution, mean values with standard deviations (SD) were used for data analysis and presentation. If the distribution was different from normal, median values and their 25th to 75th percentiles were used. Depending on the type of data distribution, the *t*-test for independent samples was used to determine differences between independent groups, whereas Mann–Whitney *U*-Test was used as a nonparametric alternative. If necessary, intragroup pairwise comparisons were made using *t*-test for dependent samples, with a nonparametric alternative being Wilcoxon matched pairs test for dependent variables, if necessary. When assessing the significance of differences and changes, $P<0.05$ was used as a threshold value.

Results

The patients in the retrospective group were included in the study according to the criteria for septic shock diagnosis accepted at that time, and all included patients had baseline low values of mean arterial pressure (on average, less than 60 mm Hg). However, they had satisfactory cardiac performance with mean stroke volume index over 50 ml/m^2 (cardiac index up to 4.1 l/min/m^2), with arterial blood lactate level over 2 mmol/L, mean

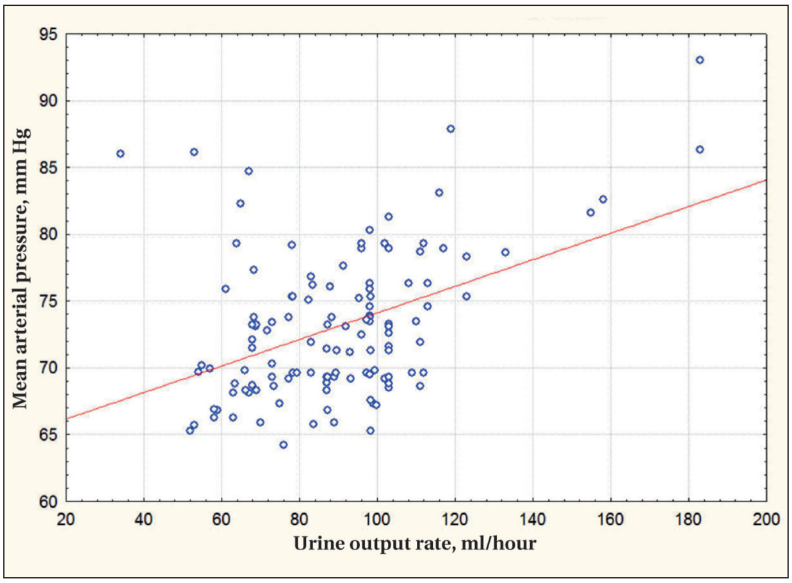

Fig. 1. Linear regression analysis of the correlation between urine output rate and MAP upon achieving a GFR>60 mL/min in the general patient cohort.

central venous blood saturation not exceeding 61.8% and global end-diastolic volume index reaching 1000 ml/m². The extravascular lung water index (EVLWI) was more than 12 ml/kg. At the baseline, most patients had a dramatic decrease of total peripheral vascular resistance index (TPVRI), which was significantly lower than 1000 dyn×sec×cm^{-5}/m². The total volume of intravenous fluid by that time (over a period of 60–120 minutes from the discovery of hypotension) was 1105.6 (SD 210.4) ml. The mean dose of norepinephrine vasopressor support was 0.19 µg/kg/min (SD 0.39). During the retrospective phase of study, renal function was assessed based on glomerular filtration rate (GFR) using data from biochemical analysis of daily urine 24 hours after the patients' admission to the intensive care unit. Recovery of normal urinary output and satisfactory GFR values were observed in 77 patients. Linear regression analysis of the correlation between urinary flow rate and mean arterial pressure when GFR>0 ml/min/m² was achieved in retrospective group patients revealed a positive correlation with R=0.81. Remarkably, the values of mean arterial pressure corresponding to recovery of GFR were significantly higher (75.2 mm Hg [SD 13.4] vs. 68.8 mm Hg [SD 11.3]) in patients with hypertension (AH subgroup). The urine output rate was also higher (Fig. 1). No significant differences in norepinephrine dosages were found.

By the end of day 1 of follow-up, normalization of both volumetric and dynamic parameters of central hemodynamics was noted in patients with satisfactory GFR. The maximum value of mean arterial pressure corresponding to restoration of satisfactory renal function was 87.9 mm Hg. The values of mean arterial pressure and total vascular peripheral resistance were significantly higher compared with the baseline. There were no significant differences in central hemodynamic parameters (CI, TPVRI, CVP, SVV, ITBVI, EVLWI) between patients with and without hypertension in the retrospective group. Organ dysfunction subsided with almost complete recovery of the vital functions on days 5–7 of follow-up.

In the remaining patients (n=44, 39.6%), renal function had not recovered by day 1 of follow-up. During days 1–2 of treatment, they received renal replacement therapy (average time of initiation was 26.4 hours after the diagnosis of septic shock), in accordance with the current local protocols. All patients received prolonged veno-venous hemo(dia)filtration (20–35 ml/kg/hour) with positive clinical effect in 36 patients, which manifested as relative stabilization of hemodynamic parameters and respiratory status during days 2–3.

Eight patients in the retrospective group failed to achieve mean arterial pressure values greater than 65 mm Hg. Arterial hypoxemia in these patients was more severe with a decrease in the oxygenation index to 142.32 mmHg (SD 12.05). Global end-diastolic volume did not exceed 700 ml/m², and EVLWI was below 10 ml/kg, stroke volume variability reached 23% (SD 3.9%). All these patients received fluid therapy within the first hour of stay in the department with an average volume of 1000 ml of crystalloid solutions according to the then-current principles of early targeted therapy to stabilize hemodynamics. Subsequent cardiac index values remained extremely low, and the total peripheral vascular resistance exceeded 2000 dyn/sec/cm^{-5}/m² in all cases. Left ventricular contractility was under 1000 mmHg. These values were the reason for prescribing dobutamine in doses from 2.5 to 11 mcg/kg/min together with the vasopressor support (norepinephrine up to 3 mcg/kg/min). Despite the subsequent significant increase of cardiac index, decrease of arterial hypoxemia severity, and lactate reduction (in some cases with the extracorporeal detoxification), these patients had EVLWI increase up to 14.7 (SD 0.24) ml/kg and increase of CVP up to 15.68 (SD 1.6) mm Hg. Low global end-diastolic volume, high variability of stroke volume, and a significant increase of total peripheral vascular resistance index were observed during the follow-up. However, no significant increase of blood pressure was noted. Lactate level remained high. All patients with a similar hemodynamic pattern died later. Mean GFR in those patients did not exceed 4.3 (SD 16.8) ml/min/m².

A total of 41 patients (33.9%) died in the retrospective group by day 28 of treatment, the overall hospital mortality was 42.1%. Mean arterial pressure values were significantly higher in surviving patients than in those who later died (75.2 mm Hg [SD 4.8] versus 68.01 mm Hg [SD 7.3] at $P<0.001$).

Vasoplegic hemodynamic disturbance was most frequently observed in the patients during the prospective phase of treatment (n=30). The therapeutic strategy in such patients was based on norepinephrine at the average dose of 0.12 (SD 0.36) mcg/kg/min, which was not significantly lower than the average norepinephrine dose in the retrospective group of patients with vasoplegic circulation. No fluid therapy was administered for the early targeted treatment of septic shock due to satisfactory volumetric preload values.

Vasoplegic-hypovolemic disorders were observed in four patients. All these patients had more than 15% increase in stroke volume during passive leg raising test and responded well to fluid therapy. However, the total volume of fluid therapy during the first 24 hours of follow-up was significantly lower in the prospective patients than in the retrospective group (1605.8 ml and 2046.9 ml, respectively, P=0.027) (Fig. 2).

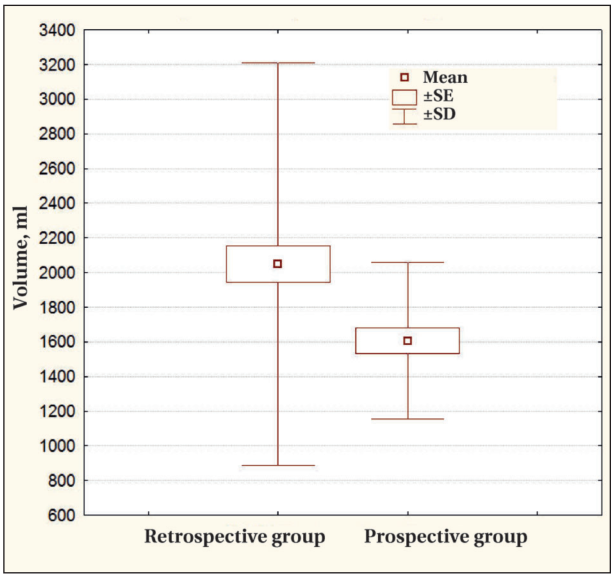

Fig. 2. Comparison of fluid therapy volumes during the first 24 hours of treatment in the retrospective and prospective groups.

Two patients included in the study at the prospective stage had a cardiomyopathic hemodynamic profile. Initially, they were hypertensive (AH subgroup) and had atherosclerotic vascular renal, coronary, and cerebral lesions.

One patient was found to develop superior mesenteric artery thrombosis during the study follow-up, which resolved during endovascular intervention. Septic shock in these patients was resistant, they demonstrated no cardiac performance improvement during the passive leg raising test. In addition to standard doses of norepinephrine and dobutamine, these patients received hydrocortisone infusion up to 200 mg per day for additional hemodynamic correction. In all patients, glomerular filtration rate was determined every 4 hours of follow-up during the prospective phase of the study. By 12 hours of follow-up, 22 patients (59.5%) had satisfactory GFR. Different therapeutic strategies were used depending on hemodynamic type until satisfactory mean arterial pressure was achieved. The MAP was increased based on the retrospective data. Average MAP in patients without hypertension was 80.7 (SD 10.4) mm Hg, in patients with baseline hypertension (AH subgroup), 82.4 (SD 9.7) mm Hg (differences were insignificant at $P \geqslant 0.05$). In one patient from the AH subgroup normalization of GFR was achieved at MAP of 101 mmHg. However, patients in the AH subgroup had significantly higher values of total peripheral vascular resistance index, while their extravascular lung water index was lower. Taking into account the retrospective data, further increase in mean arterial pressure had no clinical perspective with regard to restoration of adequate renal function. Meanwhile, as in patients in the retrospective group, there was a weak positive correlation between the urine output rate and glomerular filtration rate (Fig. 3).

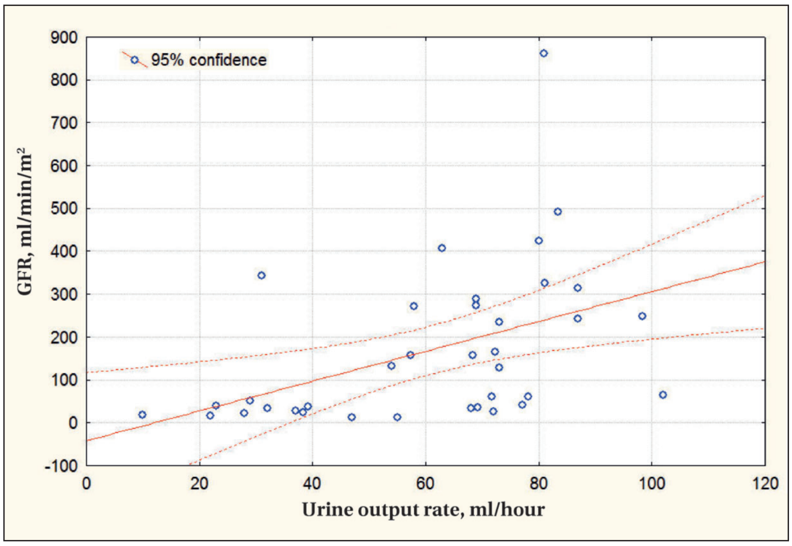

Fig. 3. Paired correlation coefficient between GFR and urine output rate in patients during the prospective phase of treatment, r=0,44261.

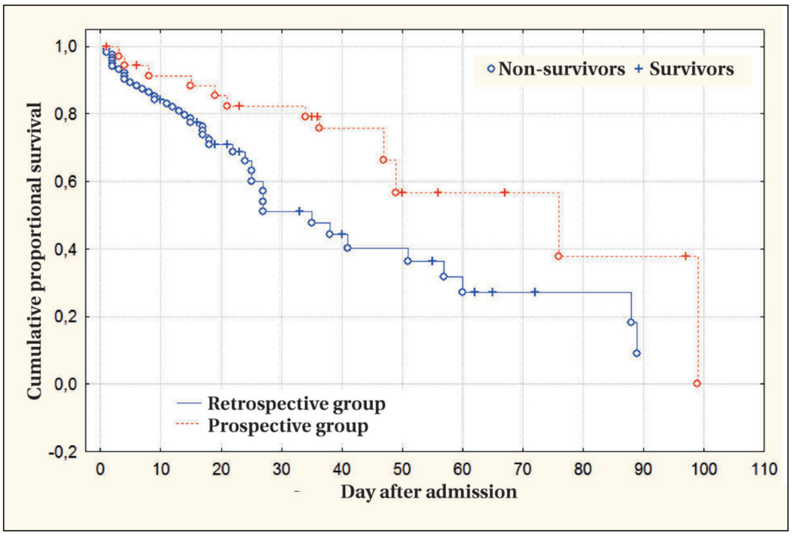

Fig. 4. Cumulative proportional survival of patients in the retrospective and prospective groups (Kaplan–Meier).

Consistent with the study design, patients with satisfactory hemodynamic and urine output rates with reduced GFR were started on renal replacement therapy (n=15 [40.5%]) after an average of 12.4 hours (SD 0.4), which was significantly earlier than in patients in the retrospective group. By 72 hours of follow-up, positive clinical effects were observed in 9 patients, in 6 patients (including 2 with a cardiomyopathic hemodynamic profile) shock was resistant. These patients died, setting the 28-day mortality in patients at the prospective stage at 16.2%, which was almost half that of the retrospective stage (33.9%). Hospital mortality in patients at the prospective stage was also significantly lower, with 11 of them dead (29.7% vs. 42.1%) (Fig. 4).

Discussion

Over the past decades, the clinical variant with relative hypovolemia and decreased cardiac performance due to reduced preload caused by fluid redistribution into extravascular space has been considered typical for patients with septic shock [32–34]. However, most patients in our study had hyperdynamic cardiovascular response along with a dramatic drop in total peripheral vascular resistance but with an adequate preload. According to national experts V. Kuzkov and M. Kirov, this hemodynamic profile corresponds to the most common septic shock course [35]. Most likely, it is associated with aggressive fluid therapy at any stage of burn treatment and corresponds to commonly shared ideas of pathogenetic treatment of burn injury, preferably at early stages. Positive fluid balance is one of the key pillars of early intensive care of burn patients [13]. Apparently, the fluid therapy being a part of the early targeted treatment of septic shock underlies a more severe illness course in patients from the retrospective group. These patients had no baseline assessment of volume status and increased preload tests, although almost all of them showed signs of increased global vascular permeability. An increase in EVLWI and worsened arterial hypoxemia were consistently noted during the following stages of hemodynamic monitoring. These changes were especially evident in those patients in the retrospective group who had cardiomyopathic and hypodynamic circulation due to the evidence of myocardial dysfunction with a total decrease in cardiac performance and increase in total peripheral resistance due to vasopressor use. In the prospective phase such patients were classified as nonresponders to the preload test. Meanwhile, those patients had a significant decrease of left ventricular contractility index (less than 1,000 mm Hg), which was regarded as a manifestation of myocardial depression associated with sepsis, and their condition was somewhat stabilized when dobutamine was administered [36]. Norepinephrine was used as the main vasopressor agent in all cases. Doses in most patients did not exceed 0.5 µg/kg/min. The duration of norepinephrine administration in patients at both study stages averaged 2.8 days (SD 0.04).

After hemodynamic stabilization in patients with septic shock, the glomerular filtration rate was restored at MAP values ranging from 65 to 101 mm Hg. The prospective phase of the study confirmed that MAP over 75 mm Hg may have nephroprotective effects in patients without baseline hypertension. Elevated MAP was not associated with adverse effects of norepinephrine. A retrospective analysis of the data showed that the lack of restoration of adequate renal function in the first 24 hours along with satisfactory values of hemodynamic parameters did not lead to the resolution of renal failure in the next two days of observation, regardless of the increase in blood pressure to threshold values. The recovery of adequate renal function occurred with significantly higher BP values. The surviving patients had significantly higher MAP values than the non-survivors.

Severely burnt patients with baseline arterial hypertension in both groups recovered adequate values of glomerular filtration rate at levels of mean arterial pressure significantly higher than in normotensive subjects. The discovery of a group of patients with abnormal hemodynamic parameters indicating myocardial dysfunction was important. Despite the evidence of hypovolemia, these patients responded negatively to the increased preload test.

Moreover, they responded with a sharp increase in the total peripheral vascular resistance index with an even greater reduction of cardiac performance when vasopressors were administered. Restoration of adequate renal function in this situation could not be achieved. Fluid therapy as a part of early targeted treatment of septic shock without prior analysis of hemodynamic abnormalities in the retrospective group led to a significant deterioration of patients. Unfortunately, all patients with this type of circulatory disorder died despite comprehensive treatment. Apparently, this hemodynamic response in septic shock was provoked by underlying severe atherosclerotic vascular lesions.

The patterns of hemodynamic abnormalities identified in patients during retrospective data analysis and individualized management at the prospective stage helped earlier determination of renal replacement therapy requirement, which together with the maintenance of optimal mean arterial pressure improved treatment outcomes.

Conclusion

Severely burnt patients with septic shock require a differentiated approach to the maintenance of mean arterial pressure for ensuring adequate perfusion of organs and tissues. The glomerular filtration rate measured using the direct Rehberg-Tareyev test could serve as a metabolic marker of renal blood flow adequacy. To determine the type of intervention for optimal hemodynamic compensation in patients with burns and septic shock, minimally invasive hemodynamic monitoring based on transpulmonary thermodilution analysis may be successfully used. Early initiation of renal replacement therapy in patients who have not restored adequate (based on the values of glomerular filtration rate) renal function within 24 hours improves the survival of patients in this group. Urine output rate alone cannot be considered as an adequate indicator of renal perfusion in severely burned patients with septic shock.

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