Research Article

JOURNAL OF HEPATOLOGY

Exploration of skin perfusion in cirrhotic patients with septic shock

Arnaud Galbois[1,2,3,*], Naïke Bigé[1,2], Claire Pichereau[1,2], Pierre-Yves Boëlle[2,4,5], Jean-Luc Baudel[1], Simon Bourcier[1,2], Eric Maury[1,2,5], Bertrand Guidet[1,2,5], Hafid Ait-Oufella[1,2,6]

[1]*AP-HP, Hôpital Saint-Antoine, Service de Réanimation Médicale, F-75012 Paris, France;* [2]*Université Pierre et Marie Curie (UPMC), Univ Paris 06, Sorbonne Universités, F-75005 Paris, France;* [3]*INSERM, UMR_S 938, CdR Saint-Antoine, F-75012 Paris, France;* [4]*AP-HP, Hôpital Saint-Antoine, Service de Santé Publique, F-75012 Paris, France;* [5]*INSERM, UMR_S 707, F-75012 Paris, France;* [6]*Paris Research Cardiovascular Center, Inserm U970, Paris, France*

See Article, pages 508–509

Background & Aims: Skin perfusion alterations are early and strong predictors of death in patients with septic shock. Cirrhosis is associated with systemic vasodilation and increases mortality from septic shock. We aimed at assessing whether the mottling score and tissue oxygen saturation (StO_2) could be used as early predictors of death in cirrhotic patients with septic shock.

Methods: This observational study included cirrhotic patients with septic shock. Each 6 h during the first 24 h, we collected data reflecting macrocirculation (mean arterial pressure, heart rate, central venous pressure, and cardiac output) and organ perfusion (arterial lactate, urinary output, $ScvO_2$, mottling score, thenar, and knee StO_2). Data of 75 non-cirrhotic patients with previously reported septic shock were used as control.

Results: 42 cirrhotic patients were included. Mortality at day 14 was 71%. At H6, parameters reflecting macrocirculation were not associated with mortality, whereas higher arterial lactate and mottling score were associated with death. Mottling score was the strongest predictor of mortality (sensitivity = 0.63, specificity = 1, OR = 42.4 (2.3–785.9)). At H6, knee StO_2 decreased in non-survivors and predicted death (sensitivity = 0.45, specificity = 1). In comparison with control, mottling kinetic was different in cirrhotic patients (delayed mottling appearance in non-survivors, earlier mottling disappearance in survivors). Knee StO_2 and skin perfusion, assessed by laser-Doppler, were higher in cirrhotic patients.

Conclusions: Mottling score and knee StO_2 at H6 were very specific predictors of death in patients with cirrhosis and septic shock. Their sensitivity was lower in cirrhotic patients due to delayed mottling appearance and higher knee StO_2 related to higher skin perfusion.

Keywords: Cirrhosis; Septic shock; Outcome; ICU; Haemodynamic.
Received 22 April 2014; received in revised form 16 September 2014; accepted 7 October 2014; available online 19 October 2014

* Corresponding author. Address: Hôpital Saint-Antoine, Service de Réanimation Médicale, 184 rue du faubourg Saint-Antoine, 75571 Paris Cedex 12, France. Tel.: +33 1 49 28 23 18; fax: +33 1 49 28 26 92.
E-mail address: galbois@gmail.com (A. Galbois).

Abbreviations: OR, odds ratio; NIRS, near-infrared spectroscopy; StO_2, tissue oxygen saturation of haemoglobin; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; SOFA score, Sequential Organ Failure Assessment score; SAPS, Simplified Acute Physiology Score; $ScvO_2$, central venous oxygen saturation.

Introduction

Septic shock, the most severe form of infection, is defined by a severe sepsis (acute organ dysfunction secondary to infection) associated with hypotension not reversed with fluid resuscitation [1,2]. Septic shock is a major health-care problem worldwide in the general population [2].

Severe infections represent one of the most dreadful complications of liver cirrhosis [3–5]. Cirrhosis has been identified as an independent risk factor of mortality in patients with septic shock (odds ratio (OR) = 2.5 [2.3; 2.8]) [5]. Despite improved outcome of patients with cirrhosis and septic shock during the last years, their mortality remains around 65% [5–7].

The identification of powerful and early predictors of death in septic shock patients is a major issue. In addition to their usefulness to give more detailed information to the patients' relatives, such predictors could be useful to suggest new resuscitation goals or to identify candidate patients for adjuvant treatments [8]. During the last years, microcirculation alterations were established as the main cause of organ failure and death [8,9] and their persistence, despite global hemodynamic resuscitation, is an earlier and stronger predictor of outcome than global hemodynamic variables [10]. Among the tools developed to assess microcirculation alteration at the bedside, we recently developed a clinical score, called the mottling score, evaluating skin perfusion [11,12]. This simple and reproducible score clinically quantifies the mottling area extension around the knee. Within six hours after the septic shock onset, the mottling score was a strong predictor of septic shock-related mortality at day 14 in patients without cirrhosis (17% for patients with no or moderate mottling, 70% for patients with mild or moderate mottling (OR = 16) and 92% for patients with severe mottling (OR = 74), p <0.001) [11]. The near-infrared spectroscopy (NIRS) measures tissue oxygen saturation of haemoglobin (StO_2), which estimates tissue oxygenation and indirectly informs about microvascular perfusion [13]. Leone *et al.* showed that StO_2 measured in the thenar eminence

was a prognostic factor in septic patients after initial resuscitation [14]. Our group recently assessed StO_2 measured in the knee area, where mottling preferentially develops, and showed that 6 h after the septic shock onset, knee StO_2 was a stronger predictor of 14-day death than thenar StO_2 [15].

Considering the very high septic shock-related mortality of cirrhotic patients, these new tools could be very useful in this population. However, to date, no study has evaluated the accuracy of microcirculation alteration to predict death in patients with chronic liver diseases and specific hemodynamic alterations [16,17]. Sheikh *et al.* recently explored the sublingual microcirculation in 45 patients with cirrhosis [18]. In patients with decompensated cirrhosis, microvascular blood flow was reduced in sublingual capillaries (10–100 μm) as compared with compensated cirrhosis. In 14 patients with cirrhosis and sepsis (without shock), the decrease in microvascular blood flow was more marked in small sublingual capillaries (10–25 μm). Interestingly, microvascular alterations were similar in patients with decompensated cirrhosis without sepsis and in non-cirrhotic patients with sepsis [18]. Therefore, we wonder whether the accuracy of the mottling score and the knee StO_2 as early predictors of death in septic shock would be applicable in patients with cirrhosis.

The main goal of this study was to assess the accuracy of the mottling score and the knee StO_2 as early predictors of death in cirrhotic patients with septic shock.

Patients and methods

Patients with liver cirrhosis

We conducted a prospective observational study in an 18-bed intensive care unit (ICU) in a tertiary teaching hospital. This hospital also includes a Hepatology unit (44 beds). During a 45-month period, from January 2009 to October 2012, all consecutive patients with liver cirrhosis, older than 18 years, admitted for septic shock, were included. Patients were considered to have liver cirrhosis in case of histological confirmation or obvious clinical, biochemical, and radiological signs. According to international criteria, septic shock was defined as a severe sepsis with a persistent hypotension despite adequate volume resuscitation and requiring vasopressors [1,2]. To avoid including patients with delayed management or with secondary worsening, we excluded patients who required initiation of vasopressors more than 24 h after admission to ICU. Patients with black skin were excluded because accurate clinical evaluation of mottling was not possible. Liver transplant recipients were also excluded.

Patients without liver cirrhosis

Seventy-five patients with septic shock without liver cirrhosis were admitted to ICU during the same period and were included in two previously published studies, assessing the prognosis value of the mottling score and the StO_2 [11,15]. Data on these patients were used as controls for assessment of the mottling score and StO_2 evolution during the first 24 h after admission to ICU.

Demographic characteristics

Usual characteristics were prospectively collected: age, gender, the primary site of infection, pathogens, cause of cirrhosis, transplantation project, Child-Pugh score [19] and the Model for End-stage Liver Disease (MELD) [20], at the admission to ICU. Severity of the septic shock was assessed by the Sequential Organ Failure Assessment (SOFA) [21] score at H6, the organ failures at H6, the CLIF-SOFA at H6 [22], and the Simplified Acute Physiology Score (SAPS) II [23] at day 1. An organ failure was defined as a SOFA score at least 3 points for the organ concerned (need for vasopressors, mechanical ventilation with a PaO_2/FIO_2 ratio $\leqslant$200, Glasgow Coma Scale score $\leqslant$9, serum bilirubin $\geqslant$100 μmol/L, serum creatinine $\geqslant$300 μmol/L or oliguria lasting for >24 h or need for renal replacement therapy, and platelet count $\leqslant$50,000/mm^3) [24].

Hemodynamic characteristics

Patients were admitted directly from the emergency department or medical wards. Circulatory support was guided by our local protocol, adapted from international guidelines [2]. Intravenous volume expansion and norepinephrine were used in a stepwise manner to achieve pre-defined endpoints of resuscitation from invasive hemodynamic monitoring: mean arterial pressure $\geqslant$65 mmHg, central venous pressure between 8 and 12 mmHg, and urinary output $\geqslant$0.5 ml/kg/h. Norepinephrine was substituted by epinephrine in case of associated systolic cardiac dysfunction as evaluated by echocardiography at bedside. Central venous oxygen saturation ($ScvO_2$) was not routinely used for shock management. Patients were included (H0) when vasopressors infusion was started (within 24 h of admission). The first 6 h are required for medical management and global hemodynamic restoration [2].

Each 6 h during the first 24 h, we prospectively collected data reflecting macrocirculation and organ perfusion. Macrocirculation was assessed using mean arterial pressure, heart rate, central venous pressure and the cardiac output (measured by trans-thoracic echocardiography). Microcirculatory dysfunction and organ perfusion were assessed by arterial lactate levels, lactate clearance, urinary output, $ScvO_2$, mottling score [11], and thenar and knee StO_2 [15]. The mottling score was previously described and validated in patients with septic shock without cirrhosis [11]. Briefly, this clinical score quantifies the extent of mottling on the legs on a 6-degree scale ranging from 0 to 5. The mottling score is based on mottling area extension on legs: score 0 indicates no mottling; score 1, a small mottling area (coin size) localized to the center of the knee; score 2, a mottling area that does not exceed the superior edge of the knee cap; score 3, a mottling area that does not exceed the middle thigh; score 4, a mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin [11]. The reproducibility of this score has been found to be excellent between observers (kappa = 0.87 (0.72–0.97)) [11]. The StO_2 was measured by the InSpectra® tissue oxygenation monitor, model 650 (Hutchinson Tech Inc, Hutchinson, MN). We used a probe with 15 mm spacing between the transmitting and receiving zones, thus allowing a measurement of StO_2 at 14 mm of depth. After at least 1 min of signal stabilization, the StO_2 was measured and recorded only if the total hemoglobin index (THI) was higher than 5, indicating a reliable signal [25]. StO_2 was measured simultaneously at two sites: thenar eminence and knee area (close to the knee at the junction between kneecap and the vastus medialis of the quadriceps) [15]. The mottling score and StO_2 measurements were performed by a senior physician who did not manage the patient; the results did not influence the individual patient treatment.

Laser Doppler assessment of skin perfusion

Skin perfusion was assessed by the laser Doppler technique (PeriScan PIM 3 System®) [26,27]. This technique has already been reported to assess skin perfusion alterations in non-cirrhotic patients with septic shock [12]. Laser light penetrates the tissue and is scattered and partly absorbed. Some of the scattered light returns to the tissue surface, where it is registered by a photo detector inside the instrument. This signal is then processed to extract the information about the microcirculatory blood flow. According to the Doppler principle, light particles that hit moving blood cells, undergo a change in wavelength/frequency (a Doppler shift), while light particles that encounter static structures, return unchanged. The perfusion can be calculated since the magnitude and frequency distribution of the Doppler shifted light are directly related to the number and velocity of blood cells. Blood perfusion is measured in Perfusion Units (PUs) and there is a documented linearity between PU and the true blood perfusion in the tissue being imaged. The penetration depth is between 0.5 and 1 mm. Data are collected by a computer and visualized as a two-dimensional colour-coded image representing varying degrees of blood flow over the scanned area. The mean blood flow is computed to yield an average of pixels in a region of interest within the scanned area using the software provided by the manufacturer (LDPIwin software). All images were collected at a setting of 4 milliseconds per pixel and most were at a maximum resolution of 255 × 255 pixels. With these settings, the total time required for a complete acquisition is approximately 5 min.

Statistical analysis

Continuous variables are expressed as median (quartile) and compared with the Mann–Whitney test. Categorical variables are expressed as counts and percentages, and compared by the χ^2-test. Survival to day 14 was assessed with a Kaplan-Meier curve and a log-rank test analysis. We chose to report 14-day mortality to have a relevant endpoint to highlight that mortality was due to the initial event, a septic shock.