Hepatic blood flow in late sepsis patients

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Background
Systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis influence total hepatic blood flow. However there are conflicting data on the time of its assessment, methodology, study design, and differentiation in terms of whether the condition is an experimental SIRS, sepsis, or a human clinical syndrome.

Objective of the study
The aim of this study was to assess the total hepatic blood flow and the contribution of hepatic arterial blood flow (HABF) and portal venous blood flow using a Doppler vascular ultrasound in SIRS, sepsis, and severe sepsis patients, aiming at a clear prognostic parameter that can predict the patient's outcome.

Results
There was a clear cutoff point of 16.09 ml/min for HABF, above which the hazard ratio for death was 5.6046, with a 95% confidence interval of 2.0078–15.6451 and a *P*-value of 0.0011 in late sepsis patients. The predictive potential for this HABF cutoff for patient mortality showed a sensitivity of 80%, specificity of 73.7%, positive predictive value of 70.6%, negative predictive value of 82.4%, 95% confidence interval of 0.612–0.907, and *P*-value of less than 0.0004. There was a significant positive correlation between the HABF and APACHE II scores ($P=0.023$). Cox regression analysis showed that only the APACHE II score and HABF were independent predictors for patients' outcome.

Conclusion
Duplex ultrasound assessment was a useful bedside method for predicting mortality in late sepsis patients through estimation of HABF, with a reasonable predictive potential at a definite cutoff level.

Keywords:
hepatic arterial blood flow, portal venous blood flow, sepsis, total hepatic blood flow

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Introduction

Sepsis is one of the main causes of death in the emergency unit and ICU. Despite improvement in the management of sepsis and related disorders, no obvious changes in outcome have been observed during the last century [1]. Many patients are recognized in the late sepsis stage [2], defined by previous investigators to be after the first 24 h of diagnosis [3]. Alteration of the hepatic blood flow in systemic inflammatory response syndrome (SIRS), early or late sepsis, and severe sepsis was a matter of interest in previous studies [3–5]. As a predictor for outcome, hepatic blood flow may be used for initial evaluation of septic patients or to assess their response to treatment [2].

Objective of the study

The aim of this study was to define hepatic blood flow changes in SIRS, late sepsis, and severe sepsis patients, aiming to predict mortality in this vulnerable group.

Patients and methods

A total of 44 individuals (22 men and 22 women) with mean ages ranging from 19 to 68 years were enrolled in this prospective study. Ten patients had SIRS, 14 had sepsis, and 10 had severe sepsis. Ten healthy individuals participated as the control group. The study was carried out in the Emergency Units of the Department of Internal Medicine of Kasr El-Ainy Hospital, Cairo University, Egypt, from March 2011 to September 2011. A bedside duplex ultrasound was used to assess the total hepatic blood flow (THBF) by measuring both the hepatic arterial blood flow (HABF) and the portal venous blood flow (PVBF) in the four groups. Death was considered as the end point in the study.

We recorded the HABF and PVBF after the clinical diagnosis for a period ranging from 2 to 50 days; therefore, all our sepsis participants were considered to be in the late sepsis stage. None of the patients were on vasopressors or positive inotropic medications. The study was approved by the ethical committee of the

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Department of Internal Medicine, and an informed consent was obtained from the next of kin.

Duplex ultrasound assessment of hepatic and portal blood flow

All patients were subjected to a substrate fast, whether oral intake for the control group or enteral or parenteral nutrition for the patients, for at least 6 h before the study.

After resting in the supine position for 10 min, both the hepatic artery and the portal vein were examined for peak systolic velocity, end diastolic velocity, vessel caliber in centimeters, and resistivity index. The wall filter ranged from 50 to 100 Hz, the angle of insonation was kept at 60° or less, and the angle correction cursor was parallel to the direction of blood flow. Blood flow in either the hepatic artery or the portal vein was measured in ml/min using Doppler spectral time-averaged mean velocity [V_{mean} = velocity time integral/time of spectral trace (s)] and vessel diameter. The blood flow volume was calculated as follows: $V_{mean} \times 60\,s \times 3.14r^2$, in which V_{mean} is in cm/s and $3.14r^2$ is the vessel area in cm^2. The hepatic artery was examined after bifurcation of the celiac trunk into hepatic and splenic arteries, just proximal to the porta hepatis.

The patients were examined for a period ranging from 2 to 50 days from diagnosis of their clinical condition, whether SIRS, sepsis, or severe sepsis.

Statistical analysis

The statistical package for the social science (SPSS Inc., Chicago, Illinois, USA), version 17 for Microsoft Windows, was used for data analysis. Quantitative variables were expressed as mean ± SD, whereas qualitative variables were expressed in percentage or number. Comparison of quantitative two-group variables was carried out using the Student *t*-test, whereas comparison between more than two groups was carried out by the analysis of variance test. The χ^2 or Fischer's exact test was used to compare qualitative variables. The area under the receiver operating characteristic curve (AUC) was used to assess the discriminatory ability of different HABF values in predicting death among sepsis patients. Associations of HABF with survival were evaluated using the Kaplan–Meier curves, followed by the log-rank test. Thereafter, the proportional hazard ratio (HR) for death was calculated according to the HABF, with a 95% confidence interval (CI), using AUC as a reference. The Cox multiple regression analysis was used for detection of independent predictors for death in sepsis patients.

Results

SIRS patients showed lower THBF compared with the control group because of lower HABF and PVBF. The HABF showed higher values in sepsis patients compared with SIRS patients and the control group, whereas the PVBF showed lower values (Table 1). There was a negative correlation between HABF and PVBF in sepsis patients (Table 2), whereas in severe sepsis patients the THBF increased because of elevation of both HABF and PVBF, with significant positive correlation between THBF and HABF and positive correlation between THBF and PVBF (Table 2). However, the positive correlation between HABF and PVBF in severe sepsis did not reach statistical significance (Table 2). HABF showed significant positive correlation with the APACHE II score ($P = 0.023$) (Fig. 1). Comparison between patients who died (25.27 ± 5.59) and those who survived (12.63 ± 3.20) as regards the APACHE II score showed a significant difference ($P = 0.001$). Similarly, comparison between patients who died and those who survived as regards HABF yielded a significant difference (24.39 ± 15.25 vs. 15.56 ± 8.44 ml/min, respectively, $P = 0.039$).

The AUC (Fig. 2) showed that a HABF cutoff value of 16.09 ml/min could predict outcome in sepsis with a sensitivity of 80%, specificity of 73.7%, positive predictive value of 70.6%, and negative predictive value of 82.4% (AUC, 0.786; SE, 0.0804; 95% CI, 0.612–0.907; $P < 0.0004$).

The patients were separated into two groups according to the cutoff point (Fig. 3) estimated by the receiver operating characteristic curve. Patients with HABF equal to or above this value (group 2; $n = 18$) showed low survival probability, whereas those with HABF below this value (group 1; $n = 16$) showed high survival probability. The predictive potential for this HABF cutoff for patients' mortality showed a sensitivity of 80%, specificity of 73.7%, positive predictive value of 70.6%, negative predictive value of 82.4%, 95% CI of 0.612–0.907, and *P*-value of less than 0.0004. Comparison of the survival curves of the two groups using a log-rank test showed a significant difference ($P = 0.0011$). The HR for death for those with HABF values of 16.09 ml/min or more was 5.6046 times those with HABF less than 16.09 ml/min, with a 95% CI of 2.0078–15.6451.

The Cox regression analysis including age, sex, stage of systemic inflammation, comorbid conditions, APACHE II score, and HABF showed that only the APACHE II score and HABF were the two independent predictors for patients' outcome.

DISCUSSION

Sepsis is the leading cause of death in ICUs in high-income countries, whereas the world global burden is suspected to be more influenced by its incidence in middle-income and low-income countries. Low-living standards, poor hygienic measures, malnutrition, and infectious diseases are presumed to precipitate sepsis in these countries. Utilizing one or more prognostic measures to anticipate the outcome is thought to be of utmost importance in countries with limited financial resources [6].

In the current study, we concluded that the increase in HABF had a significant influence on the survival of sepsis patients when it exceeded a specific cutoff point. Elevation of HABF above this particular cutoff point

Table 1 Hepatic blood flow among the four studied subgroups

	Mean ± SD				
Variables	Control	SIRS	Sepsis	Severe sepsis	*P*-value
THBF	44.36 ± 9.75	29.38 ± 2.80	39.60 ± 14.30	40.76 ± 17.90	0.07
HABF	15.19 ± 6.60	11.98 ± 3.24	24.79 ± 16.38	19.46 ± 8.51	0.03
PVBF	29.17 ± 6.64	17.39 ± 2.23	14.81 ± 4.65	21.30 ± 11.27	0.00

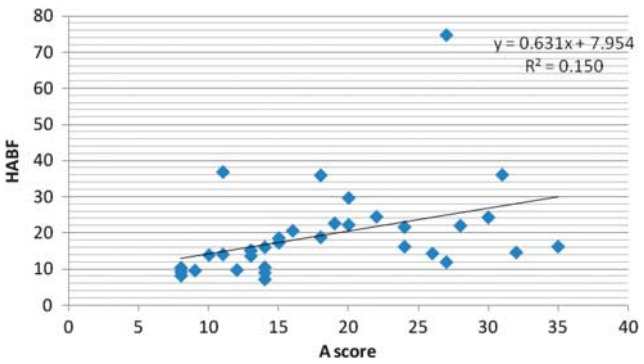
HABF, hepatic artery blood flow; PVBF, portal venous blood flow; SIRS, systemic inflammatory response syndrome; THBF, total hepatic blood flow.

Table 2 Correlation between hepatic arterial blood flow and portal venous blood flow in sepsis and severe sepsis patients

	Correlation with PVBF	*P*-value
HABF		
In sepsis	−0.560	0.037
In severe sepsis	0.630	0.051
	THBF	
Correlation with HABF	0.872	0.001
Correlation with PVBF	0.929	0.000

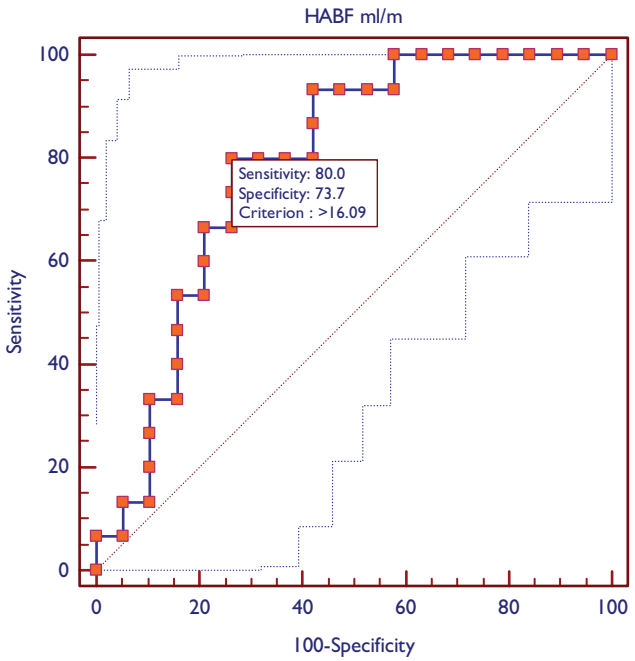
HABF, hepatic artery blood flow; PVBF, portal venous blood flow; THBF, total hepatic blood flow.

Figure 1



Correlation between the APACHE II score and HABF between all the patients' groups. A score, APACHE II score; HABF, hepatic arterial blood flow.

Figure 2



Receiver operating characteristic curve to determine HABF in predicting death among patients. HABF, hepatic arterial blood flow.

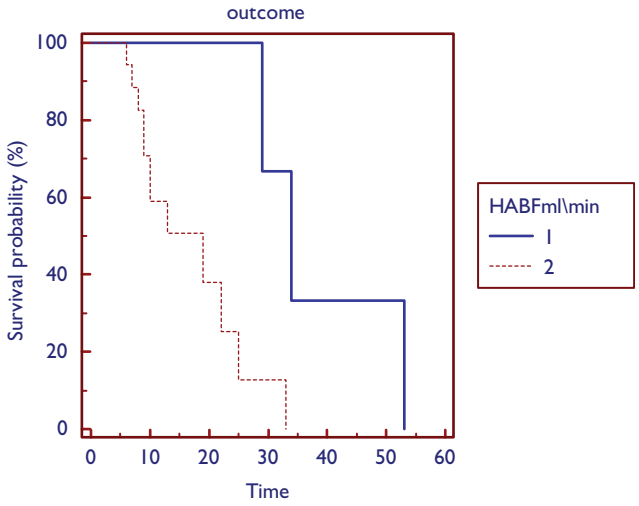
was found to have a significant predictive potential for death. Crossing this definite cutoff level of HABF was found to increase the HR for death significantly. Moreover, multiple regression analysis showed that only HABF and the APACHE II score were independent predictors for patients' outcome.

It was found that the THBF showed a significant decline in SIRS because of a decrease in both HABF and PVBF. The initial reduction in HABF observed in SIRS patients was similar to that observed in previous studies on animal models exposed to burns [4]. Secchi *et al.* [7] suggested that reduction of hepatic flow might be due to release of inflammatory mediators presumed to cause and maintain SIRS.

THBF was significantly higher in sepsis patients compared with all other groups (i.e. SIRS, severe sepsis, and control groups) because of significant increase in HABF and despite the decline in PVBF. This could be explained by the time of studying THBF, considered to be the period of late sepsis [5], which coincided with the reperfusion phase of sepsis recorded by Tadros *et al.* [4], 8 h after exposure to bacterial lipopolysaccharide injection in their animal models of sepsis. Increase in HABF during sepsis is also in agreement with previous clinical studies in which hepatosplanchnic blood flow increased significantly after injection of endotoxins in healthy volunteers [8]. This was assumed to be due to a hypermetabolic state, which was out of proportion to the increase in blood flow [9].

However, this was contradictory to the results of Varsamidis *et al.* [3], who found significant increase in HABF and PVBF in early sepsis patients but not in those with late sepsis, in whom THBF was similar to the control group. Other investigators found significantly higher THBF in sepsis patients due to elevation of PVBF and not due to increase in HABF, with the latter being lower than that observed in the control group [10]. Increase in THBF was explained by enhanced splanchnic blood flow due to the mere increase in cardiac output [11], as a result of the hyperdynamic state during sepsis [12,13], or by increased fractional splanchnic blood flow in relation to cardiac output. The normal range for splanchnic blood flow is assumed to be 15–25% of the

Figure 3



Kaplan–Meier survival curve (time in days). Group 1, patients with HABF < 16.09 ml/min; group 2, patients with HABF ≥ 16.09 ml/min. HABF, hepatic arterial blood flow.

cardiac output [14] but reached up to 57% during sepsis [15].

In the current study, PVBF was detected to be lower in patients compared with the control group, with the lowest mean value recorded in sepsis patients. An associated elevation of HABF with reduction in PVBF has been observed by previous investigators [16] and has been described as a physiological hepatic arterial buffer response by Lautt *et al.* [17], comprising a paradoxical relationship between the portal and the hepatic vascular systems; that is, if one is reduced the other dilates to compensate by increasing its blood flow [18,19]. Therefore, severe sepsis patients in the present study did not show a significant decline in THBF compared with sepsis patients, despite a significant reduction in HABF, as it was compensated by an increase in PVBF. However, the THBF was still significantly lower compared with that observed in controls. Elevation of PVBF in severe sepsis patients might be explained by successful fluid resuscitation [5]. Increase in PVBF was also observed in some studies just after intestinal mucosal barrier disruption in animal models, which was followed by acute venous congestion and edema [20]. Local inflammatory mediators such as prostaglandins [21], nitric oxide, and carbon monoxide have been claimed to increase PVBF by inducing sinusoidal relaxation [22].

HABF showed a significant predictive potential for outcome in the enrolled sepsis patients. The present study defined a cutoff level for HABF, above which mortality significantly increased in late sepsis patients represented by a significant increase in HR for death; so that, death rate in sepsis patients with HABF above 16.09 ml/min was 5.6 times higher than in those with HABF below this level. This finding might be explained by failure of the redistribution response to sepsis to redirect blood flow to crucial organs [23], with subsequent pooling of blood flow to the hepatic arterial bed. The latter might be augmented by reduced vascular resistance caused by increased nitric oxide [24]. Despite increased HABF, previous data suggest tissue hypoxia due to impaired cellular oxygen extraction [25] and enhanced local arteriovenous shunting [26]. To our knowledge, no previous studies presented in English have specified such a cutoff level. The method of hepatic blood flow assessment may be claimed to be inaccurate; however, a more accurate invasive hepatic venous cannulation method was not suitable for application in case of human sepsis [27].

In the current study, there was a significant positive correlation between the APACHE II score and HABF in the patients. Moreover both were recognized as the only independent predictors for survival by multiple regression analysis, in which age, sex, other comorbid conditions, and systemic inflammatory stage were included. The APACHE II score was seen to be an accurate predictor for mortality among sepsis patients in previous studies [28–31]. However, its positive correlation with HABF was recorded for the first time in the current study. Therefore, HABF assessment by means of a simple bedside duplex ultrasound might be used, in addition to or instead of the more complicated APACHE II score, for risk stratification of sepsis patients with a reasonable sensitivity, specificity, positive and negative predictive values.

Conclusion

The present study ascertained the THBF changes in the different stages of systemic inflammation including SIRS, late sepsis, and severe sepsis, as well as the contribution of HABF and PVBF. HABF showed a significant predictive potential for outcome in late sepsis patients, with reasonable sensitivity, specificity, positive and negative predictive values. The current study defined for the first time a cutoff point for HABF above which the HR for death increased significantly (about 5.6 times). Larger-scale studies are recommended to confirm this cutoff level and to study the influence of medications on outcome through their effect on HABF.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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