We investigated the haemodynamic response to volume depletion and subsequent repletion in patients with cirrhosis and portal hypertension. Twelve patients with compensated cirrhosis and portal hypertension were included in the study. The haemodynamic changes occurring after removal of approx. 15% of the blood volume, and subsequently after isovolume repletion with colloid, were assessed. Baseline haemodynamic measurements showed increased cardiac output and a systemic vascular resistance at the lower limit of normal. The hepatic venous pressure gradient (HVPG) was increased, at 18 mmHg. After depletion, arterial pressure, cardiac output and all right-heart-sided pressures decreased, and systemic vascular resistance increased. HVPG decreased to 16.0 mmHg. All the above changes were statistically significant. After blood volume restitution, the haemodynamic values returned to baseline. In particular, an increase in HVPG was shown in four out of the twelve patients (two with ascites and two without), which was small in three of them. However, HVPG remained the same as or lower than the baseline in the other eight patients. Patients with cirrhosis and portal hypertension exhibit an abnormal haemodynamic response to blood volume depletion. After volume repletion, no increase in the portal pressure was noted in this group of patients as a whole, although four out of the twelve patients did show an increase, possibly due to extensive collateral circulation.

INTRODUCTION

Gastrointestinal haemorrhage, in particular variceal bleeding, represents a common complication of chronic liver disease and is associated with a high mortality. Over the last decade there has been significant progress in the management of variceal bleeding. However, it is the initial resuscitation, in particular the speed and adequacy of blood volume replacement, that frequently determines the overall success of management. Studies carried out in a cirrhotic rat model have suggested that blood volume restitution following haemorrhage produces an increase in portal pressure above basal values in the animals with high portal systemic shunting (PSS) [1]. Patients with alcoholic liver disease are known to have a variable, but occasionally extensive, degree of PSS, ranging from 5 to 70% [2–4]. Should the conclusion from this animal study be valid in patients with cirrhosis, there may be important therapeutic implications with respect to volume replacement.

Key words: ascites, cirrhosis, hepatic venous pressure gradient, portal hypertension, venesection, volume repletion.
Abbreviations: CI, cardiac index; CO, cardiac output; \( \text{CO}_2 \), \( \text{O}_2 \) content; \( \text{DO}_2 \), \( \text{O}_2 \) delivery; Hb, haemoglobin; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; \( \text{PO}_2 \), oxygen tension; PSS, portal systemic shunting; PV, plasma volume; RAP, right atrial pressure; \( \text{SO}_2 \), \( \text{O}_2 \) saturation; SVR, systemic vascular resistance; \( \text{VO}_2 \), \( \text{O}_2 \) consumption.
Correspondence: Dr D. Westaby.
To our knowledge, there have been no previous reports documenting the haemodynamic response to volume depletion and repletion in patients with cirrhosis under controlled conditions. Normal subjects have been shown to tolerate a blood loss of 15–17% of the total blood volume without any evidence of haemodynamic disturbance [5]. The aim of the present study was to investigate the systemic and splanchnic haemodynamic response to blood volume depletion and isovolume repletion in patients with cirrhosis and portal hypertension.

MATERIAL AND METHODS

Subjects

Twelve patients with compensated cirrhosis (ten alcoholic/two haemochromatosis) (Child-Pugh: A, 7; B, 5) [6] and portal hypertension were included in the study. These comprised eight men and four women, with a mean age of 48.2 years (range 40–64 years). Nine of the ten patients with alcoholic cirrhosis had previously been admitted for an episode of variceal bleeding, and in all ten of them the presence of oesophageal varices was verified endoscopically. Neither of the two haemochromatotics had ever bled. Detailed medical history and clinical examination were used to exclude the presence of heart disease. Four patients were on diuretics, which were withheld 24 h prior to the study. Five patients had mild ascites. None of the twelve patients showed clinical signs of dehydration. The patients were haemodynamically stable on the day of the study, which was performed at least 7 days after the control of the presenting bleeding episode.

Written informed consent was obtained from each patient. The study was performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and was approved by the Hospital Ethics Committee.

Study design

After an overnight fast, a hepatic venous balloon-tipped catheter (Sidewinder, Cordis, Miami, FL, U.S.A.) and a pulmonary artery flotation catheter (Swan-Ganz, Edwards, CA, U.S.A.) were introduced under fluoroscopic control into the hepatic vein and pulmonary artery respectively, and an arterial cannula was inserted into the radial or femoral artery. Following a 30 min resting period, a baseline haemodynamic assessment was carried out. A volume of 600 ml, i.e. approx. 15% of the blood volume (mean 14.6%; range 13.4–17%), was then removed manually with a syringe at a continuous rate over 20 min. After another resting period of 20 min, to allow for stabilization of the haemodynamic status, all the measurements were repeated (post-depletion data). Subsequently the exact same volume, but in the form of colloid (Gelofusine), was infused over 20 min. The reason for the use of the colloid was to avoid the potential risks of haemolysis, clotting or contamination associated with the rapid withdrawal and re-infusion of the venesected blood. At 15, 30 and 60 min after repletion was completed, the measurements were repeated. Plasma volume (PV) measurements were carried out prior to the study using $^{131}$I [7], and the total blood volume (TBV) was estimated by using the formula: $TBV = PV/1 – Ht$ (where Ht is haematocrit). In six of the patients with alcoholic cirrhosis, blood sampling was performed for measurement of arterial and mixed-venous (pulmonary artery) oxygen tension ($P_{aO_2}$), haemoglobin (Hb) concentration, oxygen saturation ($S_{O_2}$) and acid–base status. In five patients, arterial blood was also collected to determine the plasma concentration of catecholamines (noradrenaline and adrenaline).

Haemodynamic assessment

Mean arterial pressure (MAP) was measured from the indwelling arterial cannula. Portal pressure was determined indirectly by measuring the difference between free and wedged hepatic venous pressure [8]. Cardiac output (CO) was measured by the thermodilution method. Cardiac index (CI) was calculated by dividing the CO by the body surface area. Right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were also determined. Systemic vascular resistance (SVR) was calculated from the formula: $(MAP – RAP) \times 80/CO$. The values of all the pressures were taken from the monitor used (Hellige-Servomed). The heart rate was recorded by continuous electrocardiographic monitoring.

Metabolic assessment

Arterial and mixed-venous samples were withdrawn into heparinized syringes and analysed immediately to determine $P_{aO_2}$, Hb concentration, $S_{O_2}$ and acid–base status (Radiometry, Copenhagen, Denmark). Together with the estimates of CI, these enabled indices of O$_2$ transport and uptake to be calculated from the following formulae [9] (in which ‘$a$’ and ‘$pa$’, e.g. in $S_{aO_2}$ and $S_{paO_2}$, denote parameters for arterial and pulmonary artery respectively).

\[
\begin{align*}
(1) \ O_2 \ content \\
\text{Arterial (CaO}_2) &= (\{Hb\} \times S_{aO_2} \times 1.34) + (P_{aO_2} \times 10^{-3}) \\
\text{reference range:} \ 15–20 \ \text{ml/dl} \\
\text{Pulmonary artery (CaO}_2) &= (\{Hb\} \times S_{paO_2} \times 1.34) + (P_{aO_2} \times 10^{-3}) \\
\text{ref. range:} \ 10–15 \ \text{ml/dl}
\end{align*}
\]
Response to volume changes in cirrhotics

(2) $\text{O}_2$ delivery ($\dot{\text{D}}\text{O}_2$) = $\text{Cao}_2 \times \text{CI} \times 10^{-3}$
(ref. range: 520–720 ml·min$^{-1}$·m$^{-2}$)

(3) $\text{O}_2$ extraction ratio = ($\text{Cao}_2 - \text{CpaO}_2$)/$\text{Cao}_2$
(ref. range: 22–30%)

(4) $\text{O}_2$ consumption ($\dot{\text{V}}\text{O}_2$) = ($\text{Cao}_2 - \text{CpaO}_2$) × CI × 10
(ref. range: 100–180 ml·min$^{-1}$·m$^{-2}$)

Catecholamines

Blood for measurement of plasma catecholamine concentration was collected into a chilled lithium heparin vacutainer and centrifuged immediately, and the supernatant was divided into aliquots which were immersed in liquid nitrogen. The aliquots were then stored at $-70^\circ$C and subsequently analysed for catecholamine levels by the radioenzymic technique, as described by Brown and Jenner [10].

Statistical analysis

The results were expressed as means $\pm$ S.E.M. Statistical analysis was performed using one-way analysis of variance to compare the values of each haemodynamic parameter at the different time points. Significance between means in the analysis of variance results was tested with the $F$ test. The paired $t$ test was used to compare the changes in catecholamine levels and in the metabolic parameters assessed, and the $t$ test was used to compare differences between patients with and without ascites.

RESULTS

Baseline haemodynamic measurements showed that MAP was $87 \pm 3.6$ mmHg and the heart rate $81.8 \pm 4.3$ beats/min. All the filling pressures of the right heart (RAP < PAP < PCWP) were within normal limits ($4.2 \pm 0.7, 12.4 \pm 1.0$ and $7.3 \pm 0.9$ mmHg respectively). CO was increased ($7.3 \pm 0.7$ litres/min) and SVR was at the lower limit of normal [$0.99 \pm 0.11$ mN·s·cm$^{-5}$ ($991 \pm 105$ dyn·s·cm$^{-5}$)]. The mean hepatic venous pressure gradient (HVPG) was high in all patients ($18 \pm 1.3$ mmHg). The mean Hb concentration of the patients was $11.1$ g/dl (range $9.8–14$ g/dl). The mean PV of the patients was $48.2$ ml/kg (range $40.7–55.7$ ml/kg; reference range in our laboratory $40–50$ ml/kg). All the patients tolerated the procedure well, without any side effects.

Sequential changes in systemic haemodynamic parameters

MAP decreased significantly after venesection, and returned to baseline levels post-repletion ($86.7 \pm 3.6$, $78.6 \pm 3.0$, $88.8 \pm 3.3$, $88.8 \pm 3.7$ and $87.3 \pm 3.0$ mmHg at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; $P$ value for all time points $= 0.0012$; Figure 1). The mean heart rate did not change significantly after venesection ($P = 0.2237$). CO decreased significantly after venesection, and had returned to baseline by 30 min after repletion ($7.3 \pm 0.7$, $6.4 \pm 0.8$, $8.0 \pm 0.8$, $7.3 \pm 0.8$ and $7.7 \pm 0.8$ litres/min at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; $P < 0.00005$). SVR increased significantly after venesection, and returned to baseline levels immediately post-repletion [$0.99 \pm 0.11$, $1.09 \pm 0.11$, $0.91 \pm 0.09$, $0.99 \pm 0.10$ and $0.94 \pm 0.09$ mN·s·cm$^{-5}$ ($991 \pm 105$, $1085 \pm 115$, $914 \pm 94$, $989 \pm 97$ and $939 \pm 87$ dyn·s·cm$^{-5}$) at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; $P = 0.0038$].
RAPP, PAP and PCWP showed significant decreases after venesection, and had returned to baseline levels 15–30 min after the administration of the colloid [RAPP, 4.2 ± 0.7, 2.8 ± 0.8, 5.1 ± 0.9, 4.6 ± 0.6 and 4.1 ± 0.7 mmHg (P < 0.00005); PAP, 12.4 ± 1.0, 8.2 ± 0.8, 13.4 ± 1.0, 12.2 ± 0.8 and 12.0 ± 0.8 mmHg (P < 0.00005); PCWP, 7.3 ± 0.9, 3.4 ± 0.6, 7.5 ± 1.0, 6.9 ± 0.9 and 6.4 ± 0.8 mmHg (P < 0.00005) at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively]. PCWP and PAP were shown to be the most sensitive haemodynamic parameters in assessing the response to volume depletion.

**Sequential changes in splanchnic haemodynamic parameters**

The mean HVPG decreased significantly after venesection, but failed to return to baseline levels after volume repletion (values of 18 ± 1.3, 16 ± 1.7, 16.7 ± 1.4, 16 ± 1.3 and 16.5 ± 1.4 mmHg at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; P < 0.05; Figure 1). In Figure 2 the individual responses of the HVPG values of the 12 patients studied are presented. In four of the patients there was an increase in the HVPG at 15 min post-repletion (two patients with ascites and two without), which was maintained at the later post-repletion time points in only two of them (one with ascites and one without). In two patients the increase was by 1 mmHg, in one by 2 mmHg, and finally one patient with ascites showed an increase up to 5 mmHg above baseline. When the patients with and without ascites were analysed separately, the former had a higher baseline mean HVPG (19 compared with 17 mmHg; P > 0.05; t test), but followed the same pattern throughout the study (Table 1; Figure 2).

When the patients on diuretics were compared with those who were not, although the former had lower CO and higher SVR than the latter and showed a bigger fall in HVPG (from 18 to 14 mmHg and from 18 to 16.8 mmHg respectively), again they followed the same pattern, and in particular there was no overshoot in the HVPG in either group (results not shown).

The decrease in the HVPG was mainly due to a fall in wedged hepatic venous pressure (25.3 ± 2.2, 22.9 ± 2.4, 24.9 ± 2.2, 23.5 ± 2.0 and 23.5 ± 2.2 mmHg at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; P < 0.0014), whereas free hepatic venous pressure, although decreased significantly after venesection, contributed less to the fall (7.3 ± 1.1, 6.8 ± 1.1, 8.2 ± 1.1, 7.5 ± 1.2 and 7.4 ± 1.3 mmHg at baseline, post-depletion and 15, 30 and 60 min post-repletion respectively; P = 0.0128).

**Sequential changes in O2 transport, O2 uptake and catecholamine levels**

Blood sampling for O2 transport and uptake measurements was performed on six patients (four Child–Pugh A and two Child–Pugh B) at baseline, 20 min post-depletion and 30 min post-repletion. Mean baseline measurements for VO2, DO2 and O2 extraction ratio were within normal limits, although there were large differences in the individual values between the patients. DO2 fell significantly after venesection (from 605 ± 89 to 494 ± 86 ml·min⁻¹·m⁻²; P = 0.002), mainly as a result of the decrease in CO, and returned to baseline after volume repletion (555 ± 104 ml·min⁻¹·m⁻²), despite a drop in the Hb concentration of 1.0–1.5 g/dl due to the haemodilution following the substitution of the removed blood with colloid. VO2 remained virtually unchanged after venesection (127 ± 20 to 125 ± 16 ml·min⁻¹·m⁻²), despite

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**Table 1. Changes in HVPG in patients with and without ascites**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Baseline</th>
<th>20 min PD</th>
<th>15 min PR</th>
<th>30 min PR</th>
<th>60 min PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ascites</td>
<td>17 ± 5.7</td>
<td>15.1 ± 5.9</td>
<td>16 ± 4.6</td>
<td>15.9 ± 4.9</td>
<td>16.1 ± 5.2</td>
</tr>
<tr>
<td>Ascites</td>
<td>19 ± 2.7</td>
<td>17 ± 5</td>
<td>19.2 ± 4.8</td>
<td>17.4 ± 3.9</td>
<td>18.2 ± 4.5</td>
</tr>
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</table>
the decrease in $D_{O_2}$, due to a significant increase in the $O_2$ extraction ratio (from 21.5 ± 2.5 to 27.1 ± 3.2%; $P = 0.03$). In two of the patients (one Child–Pugh A and one Child–Pugh B), the increase in $O_2$ extraction ratio was inadequate, resulting in a 10% drop in $V_{O_2}$ (Table 2).

Catecholamine levels were measured in five patients. Mean baseline catecholamine levels were within normal limits, as expected in patients with compensated liver disease [noradrenaline, 0.73 ± 0.13 μg/ml (reference range 0.2–0.8 μg/ml); adrenaline, 0.132 ± 0.029 μg/ml (reference range 0.02–0.2 μg/ml)]. The plasma noradrenaline concentration increased significantly after depletion to 1.0 ± 0.15 μg/ml ($P = 0.02$), and returned to baseline after repletion (0.77 ± 0.13 μg/ml), whereas the adrenaline concentration remained unchanged throughout the study (Table 3).

### DISCUSSION

The response to volume depletion is complex, involving various mechanisms that aim to maintain adequate organ perfusion. In the initial phase of a haemorrhage, the low- and high-pressure baroreceptors (which function by a continuous generalized inhibition of the sympathetic nervous tone) are unloaded, as a consequence of decreased venous return and a lowered pulse pressure, resulting in sympathetic stimulation. In the presence of more profound haemorrhage, the chemoreceptors are stimulated by a lowered pH and $P_{CO_2}$. The net effect of these reflex changes is an increase in vascular resistance in the splanchnic region. The vasoconstriction is mainly of nervous origin, but may also be mediated by the release of antidiuretic hormone and angiotensin [11]. Approx. 20% of the blood volume may be removed from an animal before significant effects on overall cardiovascular homeostasis occur.

Venous compliance of the blood reservoir is a major factor influencing cardiac preload. Splanchnic venous compliance seems to be controlled primarily through sympathetic innervation [12,13] and not passively following changes in the arteriolar vascular bed [14]. In cats and dogs, all three components of the splanchnic bed, i.e. liver, intestine and spleen, are important as a blood reservoir [12,13]. In humans the spleen seems to be relatively unimportant, and the liver and intestine appear to be the major blood reservoirs. In normal human subjects it has been shown that up to 40% of the splanchnic blood volume may be mobilized into the systemic circulation to cope with blood loss [5].

There are no data with respect to the response to volume depletion in patients with cirrhosis; however, taking into consideration the splanchnic haemodynamic disturbance of these patients [15], one might anticipate an abnormal response. In the only published study attempting to address this question, it was shown that lymph drainage in excess of 600 ml resulted in a decrease in systemic blood pressure, with a parallel decrease in portal pressure [16]. Unfortunately, that study was carried out during acute variceal bleeding, and therefore it was difficult to assess the baseline vascular volume and to compare subsequent changes. In the present study, significant decreases were observed in the CO and right-heart filling pressures (RAP, PAP and PCWP) after removal of a relatively small amount of blood (13.4–17% of the total volume) under controlled conditions, suggesting an impaired mobilization of the blood reservoir in patients with cirrhosis and portal hypertension. MAP fell as a result of the decrease in CO and possibly an inadequate increase in SVR (despite an appropriate increase in plasma noradrenaline levels, indicating that the afferent limb of the reflex is intact). These findings suggest impaired venous and arteriolar responses to sympathetic stimulation in these patients, and, although in accordance with previous studies [17–19], it is surprising that this should be so evident in patients with compensated cirrhosis. The failure of the heart rate to increase is worth noting, in view of the significant fall in CO and despite the increase in plasma noradrenaline levels. A possible explanation for this finding is decreased sensitivity of the $\beta_1$-adrenoceptors of these patients,

<table>
<thead>
<tr>
<th>Table 2: Sequential changes in $O_2$ transport and uptake</th>
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<tbody>
<tr>
<td>Values are means ± S.E.M. from six patients. Significance of differences compared with baseline values: &quot;P = 0.02; &quot;P = 0.03 (paired t test). PD, post-depletion; PR, post-repletion.</td>
</tr>
<tr>
<td>Hormone concn. (μg/ml)</td>
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<tr>
<td>-------------------------</td>
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<tr>
<td>Noradrenaline</td>
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<td>Adrenaline</td>
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<th>Table 3: Sequential changes in catecholamine levels</th>
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</thead>
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<tr>
<td>Values are means ± S.E.M. from five patients. Significance of difference compared with baseline values: &quot;P = 0.02 (paired t test). PD, post-depletion; PR, post-repletion.</td>
</tr>
<tr>
<td>Hormone concn. (μg/ml)</td>
</tr>
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</tr>
<tr>
<td>Noradrenaline</td>
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<td>Adrenaline</td>
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although there are conflicting reports in the literature on this subject [19–21]. In the study of MacGillchrist et al. [19], no difference was found in the haemodynamic response to isoproterenol (isoproterenol) between cirrhotic patients and controls, but there may be a different response to physiological sympathetic stimulation and to exogenous administration of a β-adrenergic receptor agonist.

The data with respect to oxygen transport and uptake in the six patients in whom this was measured showed an expected increase in the O₂ extraction ratio as a response to the decrease in DO₂, resulting in an unchanged VO₂. Hence tissue hypoxia was not observed in these patients, and it is very unlikely that such an effect might have interfered with the haemodynamic response to venesection.

The absence of a control group is a weakness of the present study, but it was thought unethical to perform such invasive investigations in patients who did not need them and who would not benefit from them. In the only published report in eleven healthy male volunteers [5], 17% of the estimated blood volume was removed in 30 min, and haemodynamic measurements were repeated 30 min afterwards. Following the end of the study, part of the blood and 200 ml of normal saline were re-infused. Venesection produced significant decreases in splanchnic blood volume and haematocrit. The splanchnic vascular resistance did not change, suggesting that the decrease in splanchnic blood volume was due to active vasoconstriction only. MAP and CO₂, as well as the heart rate, did not change.

The decision to replace the venesected blood with colloid was based upon safety considerations. The rates at which venesection and repletion were carried out were dictated by the limited time for which patients would tolerate the catheter table (2–2.5 h, from our previous experience). Rates of venesection and repletion of up to 50 ml/min run the risk of haemolysis and coagulopathy. Gelofusine has a half life of 4 h and a molecular mass profile that results in the majority remaining within the vascular space [22]. Adequate volume repletion in the present study is strongly supported by the return of the CO₂, right-sided pressures and systemic blood pressure back to baseline levels. Similarly, noradrenaline levels also returned to baseline values after repletion. A change in blood viscosity occurred, but it is unlikely that this had a significant impact on the results, as judged by the changes in the SVR, which returned to baseline immediately after repletion and was maintained at this level until the end of the study.

Previous experiments in a portal hypertensive rat model [23], supported by a study in cirrhotic rats with extensive PSS [1], suggested that blood restitution after haemorrhage causes a rebound increase in portal pressure above baseline values, due to a persistent increase in the collateral vascular resistance. This did not happen in the rats with a low degree of PSS. It has been suggested that such a rebound increase in portal pressure might be responsible for episodes of early rebleeding during the period of volume expansion. In another study in non-cirrhotic and cirrhotic rabbits with a variable degree of PSS [24], it was shown that only rabbits with portal vein ligation and a high degree of PSS (84%) exhibited an overshoot in the portal pressure after isovolaemic haemorrhage and re-infusion of the shed blood. In contrast, rabbits with cirrhosis induced by carbon tetrachloride or common bile duct ligation (PSS of 1.0% and 21.7% respectively) did not show any rebound increase in the portal pressure.

The overall results of the present study do not support a rebound increase in the portal pressure, at least in the majority of patients with relatively well compensated cirrhosis (Child–Pugh A and B), despite the previously reported potential for a high degree of PSS in alcoholic cirrhotic patients [2–4]. It may be speculated that these patients do not develop such an extensive PSS to be at risk from a rebound elevation in portal pressure. A second, extremely important, aspect of this study is the documented impairment of the haemodynamic response to volume depletion in cirrhotic patients, which may play a significant role in the high mortality of variceal bleeding, and emphasizes the need for prompt isovolume repletion.

REFERENCES


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