

Renal and circulatory effects of large volume plasma expansion in patients with hepatorenal syndrome type 1 (◆)

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ABSTRACT

Introduction. Hepatorenal syndrome type I (HRS I) may be a consequence of circulatory dysfunction in cirrhotic patients with portal hypertension. This uncontrolled interventional pilot study examines the hemodynamic and renal effects of large volume plasma expansion in HRS I. **Material and methods.** 14 cirrhotic patients (8 m, 6 f, age 60 (58-65) years) with HRS I received large volume plasma expansion with up to 400 mL of 20% human albumin solution per 12 over 48 h under hemodynamic monitoring by transpulmonary thermodilution. Creatinine clearances (CICreat) were calculated for 12-h periods. Plasma expansion was withheld if criteria of volume overload [Extravascular lung Water Index (ELWI) > 9 mL/kg or Global End-Diastolic Volume Index (GEDVI) > 820 mL/m²] were met. Paracentesis was performed according to clinical necessity and treatment continued for 48 h thereafter. Serum creatinine values were observed for 12 days. **Results.** Patients received 1.6 (1.5-2.0) g of albumin per kg bodyweight and day for 48 to 96 h. During the treatment period, GEDVI [724 (643-751) mL/m² vs. 565 (488-719) mL/m²; p = 0.001], cardiac index (CI) [4.9 (4.1-6.15) L/min/m² vs. 3.9 (3.4-5.0) L/min/m²; p = 0.033], urinary output [25 (17-69) mL/h vs. 17 (8-39) mL/h; p = 0.016] and CICreat [20 (15-47) vs. 12 (6-17); p = 0.006] increased whereas systemic vascular resistance index (SVRI), plasma renin activity (PRA) and plasma aldosterone were significantly reduced. At 48 h there were two complete responses (serum creatinine < 133 µmol/L) and on day 12, 8 patients had a complete response. **Conclusion.** HRS I may respond to large volume plasma expansion with or without paracentesis.

Key words. Hepatorenal syndrome. Plasma expansion. Arterial vasodilation hypothesis. Hemodynamic monitoring.

INTRODUCTION

Cirrhosis and portal hypertension cause splanchnic vasodilation, pooling of blood in the splanchnic vascular bed and a reduction of central blood volume.¹⁻³ Compensatory activation of endogenous vasopressor systems, namely the renin-angiotensin-aldosterone-system, the vaso-

pressin-system and the sympathetic-nerve-system, aims at maintaining normal blood pressure. The splanchnic system escapes the vasopressor effect, but renal vasoconstriction causes a shift in the relation between renal perfusion pressure and renal blood flow. At any given renal perfusion pressure glomerular filtration is reduced.⁴ With further deterioration of circulatory derangement, renal vasoconstriction increases and subjects patients to a high risk of acute pre-renal kidney failure, occurring either spontaneously, or after hemodynamic insults. After exclusion of intra-renal causes and simple hypovolemia, this specific type of kidney failure is termed hepatorenal syndrome (HRS). According to severity and abruptness of onset, two types have been distinguished. The more severe form, type I, carries a dismal prognosis and impairs outcome even after liver transplantation.^{3,5} Therapeutic strategies involve vasopressor therapy in combination with albumin substitution, pla-

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cement of transjugular porto-systemic shunts or extracorporeal liver support. We performed this prospective uncontrolled pilot study to investigate the possible role of plasma-expansion with large volumes of hyperoncotic human albumin solution in patients with HRS I using invasive hemodynamic monitoring in an intensive care setting.

MATERIAL AND METHODS

All cirrhotic patients with an acute increase in serum creatinine to levels of $221 \mu\text{mol/L}$ treated in our department were screened. To be included patients had to fulfill the major criteria of the International Ascites Club's 1994 definition of hepatorenal syndrome. More specifically, patients were required to have had documented normal serum creatinine values within 2 weeks prior to evaluation and had to be free of diuretics for > 48 h, and free of NSAR drugs and aminoglycosides for 2 weeks. Patients who responded with a decrease of serum-creatinine of more than $> 50\%$ or to a level below $221 \mu\text{mol/L}$ during the two days before inclusion where they received at least 1.5 L of isotonic saline plus 40 g of albumin as a 20% solution per day, were excluded, as were patients with concurrent hemorrhages or infections, a history of cardiac insufficiency or malignant disease.

Informed written consent was obtained according to the study protocol approved by our institutional ethics committee. Patients had a central venous line inserted into the right or left internal jugular vein, a thermistor-tipped arterial line inserted in one of the femoral arteries and received a urinary catheter for continuous sampling of urine. A commercially available system for pulmonary thermodilution was connected to the arterial and central venous lines (PiCCO, Pulsion Medical Systems, Munich, Germany).

Thermodilution measurements

Patients were studied in supine position, with zero pressure at the midaxillary line. Central venous pressure (CVP) was recorded at end-expiration; thermodilution measurements were done in triplicate and averaged. Parameters were indexed to body surface area, or body weight in the case of Extravascular Lung Water Index (ELWI).

Paracentesis and associated measurements of intra-abdominal pressure

Paracentesis was performed using a left lateral or infra-umbilical approach using a 5-Charriere Teflon catheter with side-holes. Intra-abdominal pressure was measured by connecting the drainage tube to a pressure transducer zeroed at the level of the midaxillary line. Pressure was read at end-expiration, after normal ventilatory modulations had been assured and with the patient in a comfortable, relaxed position.

Laboratory measurements

Standard laboratory parameters were measured according to the standards of our department of clinical chemistry. Aldosterone (ALD) was measured by competitive radio-immuno assay (RIA) (DPC, Bad Nauheim, Germany), plasma renin activity (PRA) was determined by quantitative measurement of angiotensin-I in plasma (RIA, DiaSorin, Düsseldorf, Germany). N-terminal brain-type natriuretic peptide (NT-proBNP) was determined by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) and plasma norepinephrine (NE) by high-performance liquid chromatography with electronic detection (Chromsystems, Munich, Germany).

Study protocol

After inclusion, patients were transferred to the intensive care unit. Blood was taken for baseline laboratory parameters. 12-h collections of urine were commenced and continued during the treatment period, with blood drawn at the end of each 12-h interval, for the assessment of creatinine clearance (ClCreat), fractional excretion of sodium (FeNa) and measurement of PRA, ALD and NE. At the beginning of each 12-h period, a thermodilution measurement was performed. Thereafter, two fluid challenges of 200 mL of 20% human albumin solution were administered within two hours and hemodynamic measurements were repeated afterwards.

Fluid challenges were to be withheld if GEDVI was larger than 820 mL/m^2 (normal range $680\text{-}800 \text{ mL/m}^2$), EVLWI was above 9 mL/kg (normal range $3\text{-}7 \text{ mL/kg}$) or if there were clinical signs or symptoms of pulmonary edema. As some studies report a negative impact of paracentesis on kidney function,^{6,7} it was deemed unethical to perform paracentesis in all patients as part of the protocol. Ins-

tead paracentesis was performed only if clinically necessary because of abdominal discomfort or respiratory impairment. To avoid any risk for further renal deterioration paracentesis was accompanied by the administration of 200 mL of 20% human albumin solution. Additional albumin solution was given in 100 mL aliquots to ensure a dose of at least 8 g of albumin per liter of ascites removed. Hemodynamic monitoring was maintained for 48 h after paracentesis with continuation of the 12-h pattern of urine collection and hemodynamic and laboratory investigations. In addition, four hours after the beginning of paracentesis another hemodynamic analysis and laboratory tests were performed to assess the immediate consequences of large-volume paracentesis.

After the end of the treatment period, patients were discharged from ICU and observed for the rest of their hospital stay. In patients not improving during the treatment period, vasopressor treatment with terlipressin was instituted at the discretion of the treating physicians. Daily laboratory investigations were performed. The primary end-point of the study was complete response of HRS I, defined as a serum creatinine of $< 133 \mu\text{mol/L}$, at day 12 after inclusion. Partial response was defined as a 50% decrease in serum creatinine to a value above $133 \mu\text{mol/L}$.

Statistical analysis

Because of the small sample size, non-parametric tests were used for the comparison of data at the beginning and end of the treatment episode. The Wilcoxon test was used for continuous and the Chi-square test for nominal data. The Mann-Whitney-U test was used for comparisons between groups. Correlations between selected renal, hemodynamic and humoral parameters at baseline, and their relative changes during treatment were assessed using the Spearman rank correlation coefficient. All calculations were performed with SPSS 19 for MAC. All comparisons were two-tailed and significance was assumed at $p < 0.05$.

RESULTS

From August 2005 until September 2007 68 patients with cirrhosis and renal failure were screened. 54 were excluded for the following reasons; sepsis (13); ongoing gastrointestinal hemorrhage (8); pre-existent renal impairment (4); response to withdrawal of diuretic drugs and/or fluid substitu-

tion with saline or up to 40 g of albumin as 20% solution per day (33). 14 patients had persistently elevated serum creatinine above $221 \mu\text{mol/L}$, fulfilled the above-mentioned criteria and were included. Their baseline data are presented in table 1.

Outcome and response of renal function

There were two complete responses after 48 h. At day 7, 2 patients had a partial and 4 a complete response. At day 12, 2 patients showed a partial response and 8 a complete response. Of the non-responders, three were anuric and had to be treated by continuous veno-venous hemofiltration over 5, 7, and 24 days. In one of these, renal function normalized, another one died of an intercurrent pneumonia after a failed attempt to improve renal function with terlipressin. The third patient developed chronic renal insufficiency despite therapeutic intervention with terlipressin, received intermittent hemodialysis but died after 86 days from hepatic failure. In another non-responding patient, treatment

Table 1. Demographic and clinical parameters at inclusion and parameters of outcome.

Parameters	
Age (years)	60 (56-65)
m/f	8 (57%)/6 (43%)
Child-Pugh-Score	11 (10-12)
Child-Pugh-classification	
B	3 (21%)
C	11 (79%)
Etiology of cirrhosis	
Alcohol	11 (79%)
Cryptogenic	2 (14%)
Hepatitis B	1 (7%)
Serum-creatinine ($\mu\text{mol/L}$)	256 (222-380)
Serum-bilirubin ($\mu\text{mol/L}$)	77 (37-287)
Serum-sodium ($\mu\text{mol/L}$)	127 (122-133)
Serum-osmolarity ($\mu\text{mol/L}$)	286 (269-290)
Hemoglobin (g/dL)	9.2 (7.7-10.0)
Aspartate Aminotransferase (U/L)	76 (39-121)
Alanine Aminotransferase (U/L)	36 (19-57)
Partial response at 48 h	0
Complete response at 48 h	2 (21%)
Complete response at day 7	6 (43%)
Complete response at day 12	8 (57%)
30-day survival	11 (79%)
Median transplant-free survival (days), (95% CI)	58 (21-95)

with terlipressin was successful and serum creatinine remained normal after the patient had undergone orthotopic liver transplantation. Overall, four patients received a liver transplant 30, 58, 90 and 154 days after enrolment. Median transplant-free survival was 58 days.

Plasma expansion, hemodynamics and renal function

During the treatment period that lasted between 48 and 96 h, depending on the necessity and time of paracentesis, patients received 1.6 (1.5-2.0) g of albumin per kg bodyweight per 24 h. In 5 patients one or more doses of albumin had to be withheld because of dyspnea and clinical signs of fluid overload (n = 3), EVLWI of 10 mL/kg or higher, or a GEDVI larger than 820 mL/m².² Hemodynamic parameters, laboratory values and parameters of renal function at the beginning and end of treatment are presented in table 2. Responders (n = 9) vs. non-responders (n = 5) had a significantly higher initial ClCreat [15 (10-24) mL/min vs. 8 (2-11) mL/min] (p = 0.048), but there were no significant differences between the two groups for any other hemodynamic or laboratory parameter at baseline. Changes in hemodynamic parameters during the treatment period were also not significantly different between responders and non-responders.

Correlations between humoral, hemodynamic and renal parameters

At baseline, significant correlations were found for GEDVI and FeNa (rho = 0.710; p = 0.004), CI and SVI (rho = 0.609; p = 0.021) and a significant inverse correlation for SVRI and CI (rho = -0.605; p = 0.022) and for. During the treatment period, relative changes of GEDVI were correlated with relative changes of CI (rho = 0.587; p = 0.027). There were also significant inverse correlations between changes of CI and SVRI (rho = -0.601; p = 0.023) and between CI and PRA (rho = -0.545, p = 0.044).

Hemodynamic, humoral and renal effects of paracentesis and albumin substitution

In 9 patients paracentesis was performed because of respiratory impairment (n = 3) or painful abdominal distension (n = 6). A total of 7.8 (6.0-10.1) L of ascites was removed with a substitution of 9 (7-11) g of albumin per liter ascites. Hemodynamic parameters, before and after paracentesis and fluid substitution, as well as 4 and 12 h later and levels of PRA and ALD before paracentesis, at 4 and 12 h and parameters of renal function during the 12 h intervals preceding and following paracentesis are presented in table 3. In the 9 patients who underwent paracentesis, 5/9 (56%) had a complete response at

Table 2. Clinical, laboratory and hemodynamic data at the beginning and at the end of the treatment period.

Parameter	Beginning	End	P
S-creatinine (µmol/L)	270 (222-335)	243 (172-267)	0.035
S-Sodium (µmol/L)	125 (121-133)	132 (125-137)	0.005
ClCreat (mL/min)	12 (6-17)	20 (15-47)	0.006
Urinary output (mL/h)	17 (8-39)	25 (17-69)	0.016
FeNa (%)	0.034 (0.019-0.081)	0.039 (0.028-0.238)	0.055
Renin activity (ng/mL/min)	17.8 (11-39.7)	4.9 (2.3-8.4)	0.001
Norepinephrine (ng/L)	1502 (1054-2585)	1307 (807-2139)	0.221
Aldosterone (ng/L)	855 (661-1780)	457 (294-633)	0.002
NT-proBNP (ng/L)	1246 (620-2302)	5111 (4401-17841)	0.003
MAP (mmHg)	78 (73-87)	74 (67-86)	0.753
CVP (mmHg)	9 (7-14)	19 (11-23)	0.030
HR (BPM)	91 (77-103)	92 (78-98)	0.530
CI (L/min/m ²)	3.9 (3.4-5.0)	4.9 (4.1-6.1)	0.019
SVRI (dyn*s/cm ⁵ /m ²)	1241 (1124-1684)	894 (751-1235)	0.003
EVLWI (mL/kg)	6 (5-7)	9 (7-11)	0.006
GEDVI (mL/m ²)	565 (488-719)	724 (643-751)	0.001
SVI (mL/m ²)	45.7 (37.2-54.0)	52.9 (43.2-65.1)	0.041
CPI (W/m ²)	0.65 (0.51-0.87)	0.88 (0.72-1.08)	0.048

ClCreat: creatinine clearance. FeNa: fractional excretion of sodium. MAP: mean arterial pressure. CVP: central venous pressure. HR: heart rate. CI: cardiac index. SVRI: systemic vascular resistance index. EVLWI: extravascular lung water index. GEDVI: global end-diastolic volume index. SVI: stroke volume index. CPI: cardiac power index (CI*MAP/451). Data presented as median (25th-75th percentile).

Table 3. Hemodynamic, humoral and renal effects of paracentesis (n = 9).

Parameter	Before	After	4 h	12 h
IAP (mmHg)	21 (17-22)	9 (8-11)	-	-
MAP (mmHg)	83 (69-92)	66 (59-79)	76 (68-88)	80 (62-88)
CVP (mmHg)	14 (12-20)	14 (9-18)	17 (14-21)	12 (10-21)
HR (BPM)	90 (78-98)	95 (86-103)	94 (79-95)	87 (83-101)
CI (L/min/m ²)	3.9 (2.9-4.7) p = 0.028	4.8 (3.8-7.1); p = 0.021	4.6 (4.0-6.1); p = 0.038	4.6 (3.8-5.2);
SVRI (dyn*s/cm ⁵ /m ²)	1423 (951-1,736)	7586 (666-1468); p = 0.028	866 (719-1408); p = 0.028	1041 (889-1481)
GEDVI (mL/m ²)	643 (579-752)	683 (618-734)	671 (627-762)	657 (593-713)
Renin activity (ng/mL/min)	11.7 (5.9-123)	-	7.0 (4.3-32); p = 0.008	5.1 (43.0-19.6); p = 0.012
Aldosterone (ng/L)	1241 (475-1,824)	-	630 (238-947); p = 0.008	548 (250-1148); p = 0.028
ClCreat (mL/min)	12 (6-27)	-	-	17 (12-39); p = 0.011
FeNa (%)	0.039 (0.018-0.113)	-	-	0.057 (0.021-0.135)
Urinary output (mL/h)	17 (6-52)	-	-	33 (21-73); p = 0.012

IAP: intra-abdominal pressure. MAP: mean arterial pressure. CVP: central venous pressure. HR: heart rate. CI: cardiac index. SVRI: systemic vascular resistance index. GEDVI: global end-diastolic volume index. ClCreat: creatinine clearance. FeNa: fractional excretion of sodium. Data presented as median (25th-75th percentile).

12 days, in patients without paracentesis, there were 4/5 (80%) complete responses (p = 0.378).

DISCUSSION

The results of this study suggest that HRS type I may revert after large volume plasma expansion with or without paracentesis in a proportion of patients. The hemodynamic reaction to plasma expansion is compatible with a preload-driven increase of CI and SVI but we also find a decrease of SVRI and plasma renin activity and aldosterone levels, suggesting that reduced vasoconstriction and, consequently, afterload may have contributed to the increase of CI.

Hemodynamic changes were paralleled by a significant increase of creatinine clearance and urinary output.

Previous studies suggested that the reduced central blood-volume of cirrhotic patients is not amenable to plasma expansion,^{8,9} but the amount of volume infused was much smaller than in our present study. Correlated with the increase of GEDVI, seen in our patients, there was an amelioration of hyponatremia. This is in agreement with the current understanding of the pathophysiological me-

chanism leading to hypervolemic hyponatremia in cirrhotic patients,¹⁰ which attributes the impairment of renal excretion of free water to the decrease in effective blood volume and consecutive secretion of antidiuretic hormone (ADH). Neither ADH nor its surrogate parameter copeptin were measured in our study, however we hypothesize that the improvement of hyponatremia was due to a suppression of ADH secretion caused by the increase of GEDVI. This would be in accordance with the reduction of the initially massively elevated plasma renin activity, regarded as a laboratory indicator of central underfilling,¹¹ and plasma aldosterone levels seen in our patients at the end of the treatment period. These additional findings support our conclusion that plasma expansion resulted in a clinically relevant increase of effective central blood volume and cardiac preload.

The use of albumin infusions in cirrhotic patients has been established for several indications. After large-volume paracentesis, albumin infusion prevents post-paracentesis circulatory dysfunction^{6,12} and renal failure in patients with spontaneous bacterial peritonitis.¹³ In a trial combining a goal directed approach towards volume substitution in HRS-patients with vasopressor treatment, Alessan-

dria, *et al.* saw a surprisingly high proportion of patients, whose kidney function improved during a pre-run to the actual study, after albumin substitution had been titrated to achieve a CVP above 10 mmHg.¹⁴

Albumin infusions have been accepted as an essential adjunct to vasopressor treatment in HRS 1 after an earlier study on their use in combination with terlipressin.¹⁵ Published studies on vasopressor treatment of HRS employ fixed dose regimens of 20-40 g of albumin per day, sometimes loading the patient with 1 g/kg of body weight on the first two days.¹⁶ However, to our knowledge, a strategy of plasma expansion with albumin infusions alone has so far not been assessed in the treatment of HRS. Instead of a fixed dose regimen and in the absence of dose finding studies, we employed a regimen of albumin infusion limited by criteria of volume overload. This resulted in much larger amounts of albumin infused than in any other published study on the treatment of HRS.

In those cases, where paracentesis with albumin substitution was performed in our study, it resulted in an increase of CI and a drop of SVRI, but no relevant changes in mean arterial pressure (MAP) or GEDVI. As a result renal perfusion pressure (RPP) increased. PRA and plasma aldosterone levels were significantly reduced after paracentesis, whereas creatinine clearance increased.

The most recent amendment of the diagnostic criteria for HRS explicitly requires that the condition is not fluid responsive.¹⁷ Consequently, a negative trial of plasma expansion with 1 g of albumin per kilogram of body weight per day for two days is included as a prerequisite for diagnosis of HRS. Whereas all our patients fulfilled the previous diagnostic criteria of HRS, published in 1996, two patients responded within 48 h of large volume plasma expansion and we cannot exclude that they may also have responded to the lower dose of plasma expansion required by the revised diagnostic criteria of HRS-published in 2007.¹⁷ 12 of the 14 patients did not respond within 48 h to a higher dose of plasma expansion than that requested by the revised diagnostic criteria and so would have fulfilled these revised definitions for HRS type 1. We believe that current diagnostic criteria of HRS with a volume trial using an arbitrary volume of plasma expansion may result in the inclusion within the diagnosis of HRS of patients who might actually benefit from large volume plasma expansion.

Comparing responders and non-responders in our cohort, the only parameter significantly different

between both groups was baseline creatinine clearance. Worse baseline renal function has also been associated with poor response of HRS treatment with terlipressin¹⁸ suggesting that early treatment of HRS is beneficial and advanced HRS may become irreversible due to ischemic tubular necrosis. Whereas studies on the effect of treatment of HRS with terlipressin have found increases in MAP to be predictive of renal response,^{18,19} there were no significant changes in MAP in our cohort, neither in responders nor in non-responders.

The results of two recently published randomized multi-center studies on treatment of HRS with terlipressin showed response rates that were lower than those estimated by a meta-analysis incorporating both controlled and uncontrolled trials.²⁰ Furthermore, there was a high rate of serious, mainly ischemic, adverse events.^{21,22} In one of the studies, concomitant albumin substitution was directed by measurement of CVP,²¹ whereas in the other study, there was no hemodynamic monitoring except for measurement of non-invasive blood pressures and only 88% of patients received albumin.²² As CVP is not reliable as a marker of volume status in patients with elevated intra-abdominal pressure, in both studies relative hypovolemia may have been present in a proportion of patients and may explain the high rate of serious adverse events²³ and response rates that need to be improved. Interestingly, a recent meta-analysis of studies of vasopressor treatment in HRS, found a correlation of decreasing serum creatinine, decreasing PRA and increasing MAP.²⁴ This is in contrast with the findings of our study, where MAP remained unchanged despite improvements in renal function and suggests that the suppression of renal vasoconstriction in HRS I may be achieved in two ways: increase of general vasoconstriction by vasopressor treatment and improvement of cardiac output by plasma expansion.

In addition to the mono-centric design of this study and the small number of patients actually enrolled, several shortcomings limit the interpretation of our findings.

First of all, because of the lack of a control group, we cannot exclude chance improvements in renal function. However, in the light of available data on the prognosis of HRS I, and the low rates of improvement of renal function published for the control arms of recent studies on terlipressin therapy in HRS I, we think it is highly unlikely that spontaneous improvements in renal function could explain the results seen in our patients. Secondly, we cannot discriminate between effects of paracentesis and

plasma expansion. The aim of this pilot study, however, was to evaluate a possible role of large volume plasma-expansion as an adjunct in the treatment of HRS type 1. Plasma expansion will result in the necessity of paracentesis in many patients. Thus the setting analyzed in our cohort reflects clinical practice.

CONCLUSION

We believe that the concept of HRS I, diagnosed according to current criteria, as being unresponsive to plasma expansion, must be questioned. Instead, strategies of large-volume plasma expansion should be evaluated in the treatment of HRS I and future studies on combined therapy with vasopressors and plasma expansion designed with more attention to hemodynamic parameters.

ABBREVIATIONS

- **HRS I:** Hepatorenal syndrome type 1.
- **ClCreat:** Creatinine clearance.
- **GEDVI:** Global end-diastolic volume index.
- **CI:** Cardiac index.
- **SVRI:** Systemic vascular resistance index.
- **PRA:** Plasma renin activity.
- **CVP:** Central venous pressure.
- **ELWI:** Extravascular lung water index.
- **FeNa:** Fractional excretion of sodium.
- **ALD:** Aldosterone.
- **NE:** Norepinephrine.
- **SVI:** Stroke volume index.
- **RPP:** Renal perfusion pressure.
- **MAP:** Mean arterial pressure.
- **HR:** Heart rate.
- **CPI:** Cardiac power index.
- **IAP:** Intra-abdominal pressure.

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