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Original Article

Enhanced external counterpulsation: a new technique to augment renal function in liver cirrhosis

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Abstract

Background. Advanced liver cirrhosis is characterized by cardiovascular changes, such as low arterial blood pressure, peripheral vasodilation and renal vasoconstriction. As a consequence, renal hypoperfusion, impaired diuresis and natriuresis and eventual hepatorenal syndrome may ensue. Previous studies using head-out water immersion to increase central blood volume have demonstrated the functional nature of the renal abnormalities. Enhanced external counterpulsation (EECP) is a new non-invasive cardiac assist device to augment diastolic blood pressure by electrocardiogram-triggered diastolic inflation and deflation of cuffs wrapped around the lower extremities. We investigated whether EECP would improve renal dysfunction of liver cirrhosis.

Methods. Twelve healthy controls and 19 patients with liver cirrhosis were observed during 2 h of baseline followed by 2 h of EECP. The following parameters of renal and cardiovascular function were measured: renal plasma flow by *para*-aminohippurate clearance, glomerular filtration rate (GFR) by inulin clearance, urine flow rate, urinary excretion rates of sodium and chloride, mean arterial blood pressure (MAP), renal vascular resistance (RVR) and plasma concentrations of renin, atrial natriuretic peptide (ANP), endothelin-1, antidiuretic hormone, epinephrine and *N*-epinephrine.

Results. EECP was well tolerated by healthy controls and cirrhotic patients alike. EECP increased MAP (cirrhotic patients: from 74 ± 18 to 88 ± 20 mmHg, $P < 0.01$; controls: from 89 ± 8 to 94 ± 5 mmHg, $P =$ NS) and ANP (cirrhotic patients: from 23 ± 18 to 30 ± 20 ng/l, $P < 0.05$; controls: from 11 ± 4 to 16 ± 5 ng/l, $P < 0.01$). The plasma renin concentration decreased (cirrhotic patients: from 98 ± 98 to 58 ± 57 ng/l, $P < 0.01$; controls: from 4.6 ± 1.6 to 3.4 ± 1.1 ng/l, $P < 0.01$). This was associated with improvement of the urinary flow rate (cirrhotic patients: from 3.6 ± 1.8 to 4.6 ± 0.7 ml/min, $P < 0.05$; controls: from 1.8 ± 1.5 to 2.8 ± 1.9 ml/min, $P < 0.05$), as well as of the sodium and chloride excretion rates in both groups. However, in contrast to healthy controls, GFR and renal plasma flow in cirrhotic patients failed to rise significantly. Renal vascular resistance fell numerically in healthy controls (68 ± 5 *vs* 55 ± 4 mmHg · min/l; $P =$ NS). In contrast, RVR showed a significant increase by ~20% in cirrhosis (67 ± 4 *vs* 80 ± 8 mmHg · min/l; $P < 0.05$). Endothelin-1 levels fell in controls (0.38 ± 0.42 *vs* 0.31 ± 0.35; $P < 0.05$), whereas they remained statistically unchanged in cirrhotic patients. Epinephrine, *N*-epinephrine and vasopressin were not altered by EECP in either group.

Conclusions. EECP is an effective procedure to augment renal excretory function in healthy volunteers as well as in patients with cirrhosis. In healthy volunteers, GFR and renal plasma flow increased during EECP. In contrast, these parameters remained unchanged in the patients and their renal vascular resistance increased during EECP. Therefore, EECP improves diuresis, but does not influence the vasoconstrictive dysregulation of the kidneys in liver cirrhosis.

Keywords: enhanced external couterpulsation; hepatorenal syndrome; liver cirrhosis; shear stress

Introduction

Liver cirrhosis is associated with marked abnormalities of the systemic circulation. There is significant

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peripheral vasodilation and a hyperdynamic circulatory state. It is characterized by increases of cardiac output, plasma volume and splanchnic blood flow. The overall result is a decrease of mean arterial blood pressure [1,2]. In contrast, the renal vasculature is constricted and the excretion of sodium and water is impaired [3,4]. Recent evidence suggests nitric oxide as a major cause of the peripheral vasodilation in cirrhosis [5]. However, the causes of the renal vasoconstriction have remained unclear. Although vasoconstrictor systems, such as the sympathetic nervous system, the renin–angiotensin–aldosterone system and the endothelin system, are stimulated in cirrhosis and have been proposed to contribute to the renal vasoconstriction [1,6], there is as yet no convincing evidence to demonstrate their involvement directly.

We decided to use a novel procedure, enhanced external counterpulsation (EECP), to study renal blood flow in cirrhotic patients. EECP operates by electrocardiogram (ECG)-triggered diastolic inflation and deflation of cuffs wrapped around the lower extremities (Figure 1). In this way EECP augments diastolic arterial blood pressure [7]. It increases effective intra-arterial blood volume similar to intra-aortic balloon pumping or head-out water immersion. EECP, originally developed for the non-invasive treatment of cardiac patients [8], has not been tested in cirrhosis before. Since previous studies in controls indicated an increased renal blood flow velocity during EECP [9,10], we considered EECP to be a promising procedure for liver cirrhosis. In the present studies we asked two questions: (i) is EECP feasible in cirrhotic patients and is it effective in improving renal excretory function and (ii) does the renal vasculature generate a response to the increased mean arterial blood pressure that is comparable to that in normal controls?

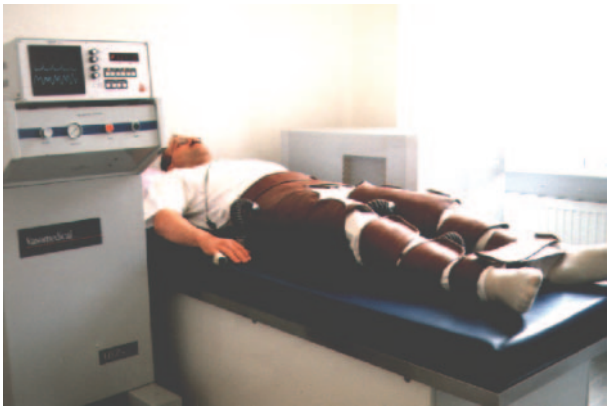

Fig. 1. Set-up of EECP. The proband is seen resting supine on the EECP table. Pneumatic cuffs are wrapped around the lower extremities.

Subjects and methods

Patients and controls

Nineteen patients with liver cirrhosis and 12 healthy controls participated in the study. The diagnosis of liver cirrhosis had been made by the hepatologist in all cases. The diagnosis was established on the basis of clinical, laboratory, sonographic and endoscopic evidence. In two patients a liver biopsy proving the diagnosis was available. Sixteen patients suffered from alcoholic cirrhosis, two from chronic active hepatitis and one from primary biliary cirrhosis. The classification of the patients according to the Child–Pugh classification is in Table 1.

As controls we studied healthy volunteers without any known cardiovascular, renal, hepatic, pulmonary or endocrine disease.

The following were used as exclusion criteria for the EECP procedure: aortic regurgitation, aortic aneurysm, atrial fibrillation, deep venous thrombosis, leg ulcer, marked peripheral oedema and a prothrombin time with an INR >2. Before the start of EECP each participant received an ECG, an echocardiogram and a duplex ultrasound study of the veins of the lower extremities.

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Technische Universität Dresden. Informed consent was obtained from all study participants according to the Declaration of Helsinki.

Study protocol

All participants abstained from food and beverages for $\geq$4 h before the beginning of the study protocol. All diuretics were discontinued $\geq$12 h before beginning EECP. All experiments were performed in the early afternoon. We placed a small intravenous catheter into a forearm vein and inserted a bladder catheter shortly before the start of the study.

The duration of the protocol was 4 h; the protocol consisted of 2 h of supine rest (control phase) and 2 h of EECP (experimental phase). The initial 2 h control phase

Table 1. General data of the cirrhotic patients and the controls

Group	Number	Age (years)	Gender (female/male)	Baseline plasma sodium concentration (mmol/l)	Number of patients with ascites	Mean dosages of spironolactone (mg/day)	Mean dosages of furosemide (mg/day)
Controls	12	24 ± 2	4/8	137.7 ± 1.7			
Child A	6	52 ± 13	2/4	137.6 ± 2.3	0	50 ± 55	0
Child B	9	57 ± 8	3/6	134.9 ± 3.4	6	89 ± 55	47 ± 42
Child C	4	52 ± 12	1/3	134.0 ± 3.0	4	88 ± 118	65 ± 44

started with a run-in period of 30 min of rest followed by 90 min of baseline observation. The period of EECP (experimental phase) again consisted of a 30 min run-in phase and a 90 min period of experimental observation. Throughout the study the participants rested supine on a specific EECP table (Figure 1). The pressure cuffs wrapped around the lower extremities were in place from the beginning of the control phase. Heart rate and beat-to-beat radial artery blood pressure readings were recorded continually by means of a vascular unloading technique (Finapress™; Ohmeda Monitoring Systems, Englewood, USA).

The EECP machine was operated by applying ECG-triggered diastolic pressure of 250–300 mmHg to the vascular bed of the calves and upper thighs by means of two air-filled cuffs (Enhanced External Counterpulsation™; Vasomedical Inc., Westbury, NY, USA). Finger plethysmography was used to record the response of blood pressure to EECP. It also served to optimize the augmentation of blood pressure during diastole by adjusting the temporal delay between the R-wave of the ECG and the onset of counterpulsation [11].

Each participant received intravenous infusions of 0.45% NaCl and of 5% glucose. Both infusions were given at a rate of 125 ml/h throughout the 4 h of study. In cirrhotic patients the infusion rates were reduced to 62.5 ml/h. Renal blood flow was determined using the renal clearance of aminohippurate sodium (MSD, West Point, USA). Following an initial bolus of 0.04 ml/kg, aminohippurate sodium was infused at a constant rate of 3.3 ml/h. The glomerular filtration rate (GFR) was determined by inulin clearance (INUTEST™; Laevosan GmbH, Linz, Austria). Following an initial bolus of 0.2 ml/kg, inulin was infused at a constant rate of 7.0 ml/h. Urine flow rate and the concentrations of aminohippurate and inulin were measured repeatedly throughout the experimental period as needed. The basic principles of the protocol are also shown diagrammatically in Figure 2.

Blood samples were taken after 45 and 90 min from the beginning of baseline and experimental observation periods. All blood samples were drawn into pre-cooled EDTA tubes, centrifuged immediately at 4°C and 3600 r.p.m. for 10 min and the supernatant was stored at −70°C until analysis. Plasma concentrations of endothelin-1, renin, atrial natriuretic peptide (ANP), antidiuretic hormone (ADH), epinephrine and *N*-epinephrine were measured. Endothelin-1 was estimated using a commercial enzyme-linked immunosorbent assay kit (Euro-Diagnostica AB, Malmö, Sweden). Reported cross-reactivity with big endothelin-1 was 6%. Concentrations of renin (ERIA Diagnostics Pasteur, Marnes la Coquette, France), ANP (Euro-Diagnostica, Arnhem, the Netherlands), ADH (DPC Biermann GmbH, Bad Nauheim, Germany) as well as epinephrine and *N*-epinephrine (IBL, Hamburg, Germany) were determined by radioimmunoassay.

Urinary volumes were determined every 30 min. Urinary excretion rates of sodium and chloride were determined by flame photometry. Urinary osmolality was measured by freezing point depression.

Statistical methods

Statistical significance comparing values before and during counterpulsation was calculated by a paired non-parametric test (Mann–Whitney *U*-test). The level of significance was considered to be $P < 0.05$.

Results

All patients and controls tolerated the 4 h procedure well. There were no drop-outs. Also, there were no adverse events.

General characteristics of patients and controls are given in Table 1. Six patients were in Child–Pugh class A, nine in class B and four in class C. Controls were younger than patients (23.7 ± 2.5 *vs* 54.4 ± 10.5 years; $P < 0.001$). At baseline, urine and sodium excretion rates as well as mean blood pressure measurements were lower in patients than in controls. The plasma concentrations of endothelin, ANP, ADH, epinephrine, *N*-epinephrine and renin were higher in patients than in controls.

An illustration of the haemodynamic changes induced by EECP is shown in Figure 3. The figure illustrates the flow velocity, as determined by duplex Doppler sonography, in the renal artery. As shown in the lower panel of Figure 3 there was an increased flow during diastole when EECP was in operation. Corresponding recordings were made by pulse wave tracing (Figure 4).

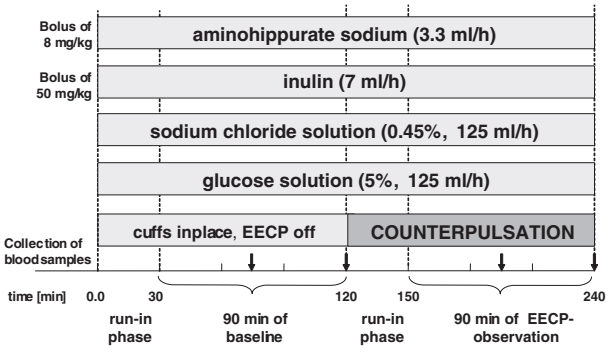

Fig. 2. Schematic representation of the study protocol.

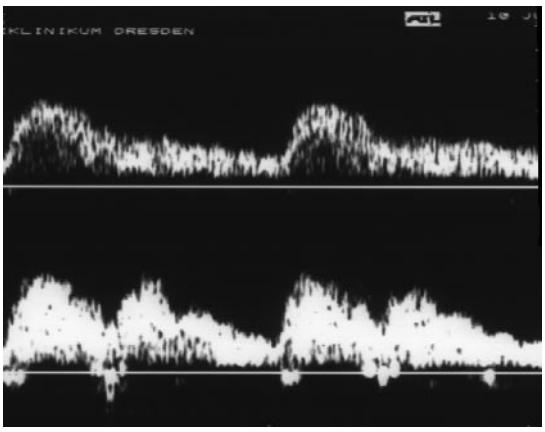

Fig. 3. Recording of renal artery blood flow as demonstrated by Doppler ultrasound at rest (above) and during EECP (below) in a healthy volunteer. The lower panel demonstrates an additional peak representing blood flow during diastole when EECP is in operation.

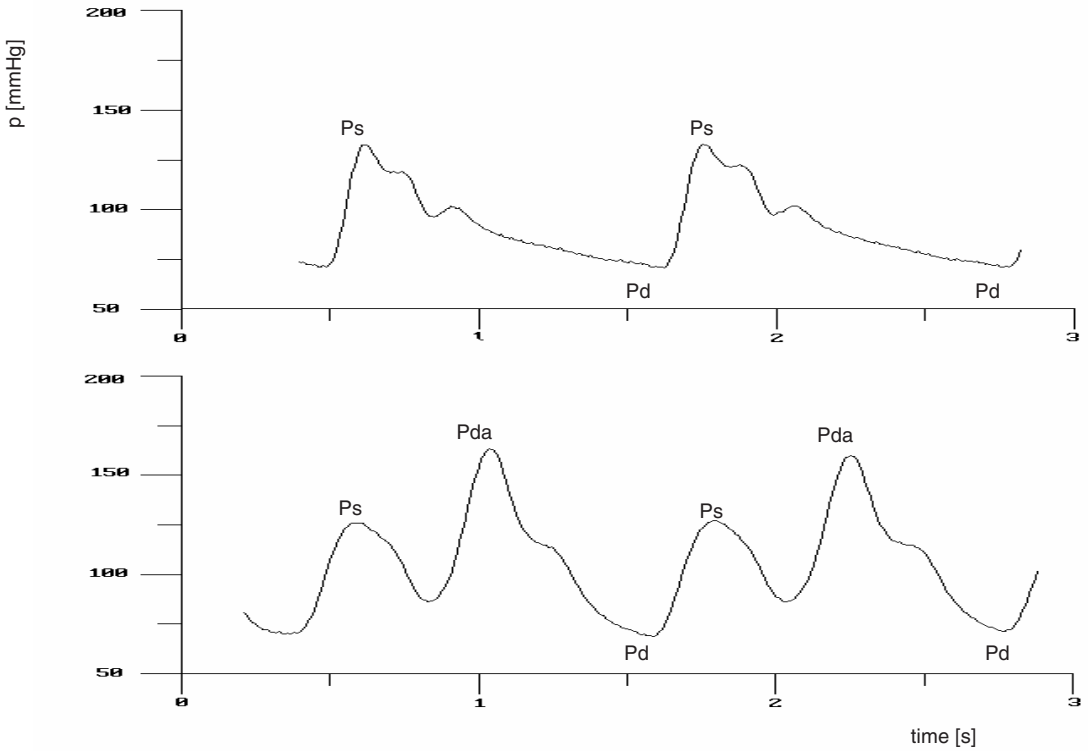

Fig. 4. Pulse wave pattern before (upper panel) and during EECP (lower panel). The pulse curve was registered by the vascular-unloading technique in the finger. Ps, systolic blood pressure; Pd, diastolic blood pressure; Pda, augmented diastolic blood pressure.

Table 2. Measured parameters of renal function and plasma levels of hormones in controls and cirrhotic patients before and during EECP

	Controls ($n=12$)		Patients ($n=19$)	
	Before EECP	2 h of EECP	Before EECP	2 h of EECP
Urinary excretion rate (ml/min)	3.6 ± 1.8	4.6 ± 0.7^{a}	1.8 ± 1.5	2.8 ± 1.9^{a}
Urinary sodium excretion rate (mmol/min)	0.20 ± 0.06	0.31 ± 0.08^{b}	0.12 ± 0.11	0.18 ± 0.15^{a}
Urinary chloride excretion rate (mmol/min)	0.12 ± 0.05	0.18 ± 0.06^{a}	0.07 ± 0.09	0.11 ± 0.13^{a}
Renal plasma flow (ml/min)	515 ± 134	676 ± 189^{a}	431 ± 134	487 ± 231
GFR (ml/min/1.73 m^2)	68 ± 16	84 ± 22^{a}	70 ± 34	71 ± 42
Urinary osmolality (mosm/kg H_2O)	487 ± 280	274 ± 69^{a}	516 ± 240	405 ± 248^{a}
Mean arterial pressure (mmHg)	89.3 ± 8.4	94.3 ± 5.1	74.0 ± 18.5	88.5 ± 20.1^{b}
Renal vascular resistance (mmHg · min/l)	68.5 ± 17.2	55.2 ± 12.5	66.6 ± 20.7	79.7 ± 37.2^{a}
Plasma renin concentration (ng/l)	4.6 ± 1.6	3.4 ± 1.1^{b}	97.6 ± 97.8	57.8 ± 52.2^{b}
Plasma ANP concentration (ng/l)	11.4 ± 4.3	16.2 ± 5.3^{b}	22.6 ± 17.9	30.2 ± 20.5^{a}
Plasma endothelin-1 concentration (pmol/l)	0.38 ± 0.42	0.31 ± 0.35^{a}	2.17 ± 0.55	2.31 ± 0.40
Plasma ADH concentration (ng/l)	3.1 ± 1.2	3.8 ± 1.3	9.7 ± 16.4	7.0 ± 12.1
Plasma epinephrine concentration (nmol/l)	0.08 ± 0.05	0.11 ± 0.01	0.53 ± 0.32	0.48 ± 0.23
Plasma norepinephrine concentration (nmol/l)	0.69 ± 0.34	0.67 ± 0.34	2.91 ± 1.70	2.82 ± 1.37

[a] $P < 0.05$; [b] $P < 0.01$.

The mean arterial blood pressure increased more in cirrhotic patients (from 74.0 ± 18.5 to 88.5 ± 20.1 mmHg, +19.6%; $P < 0.01$) than in controls (+5.6%; $P =$ NS; Table 2). The pulse rate did not change in either group during EECP. Counterpulsation was found to increase renal plasma flow by ~30% (from 515 ± 134 to 676 ± 189 ml/min; $P < 0.05$) in controls while renal plasma flow did not change in cirrhotic patients. This was surprising because mean arterial blood pressure had increased (by 19.6%) in patients but not in controls. In addition, GFR increased by 24% (from 66 ± 23 to 82 ± 22 ml/min) in controls ($P < 0.05$); however, there was no change of GFR in cirrhotic patients. We calculated renal vascular resistance. In controls it fell numerically by 20%, but this change did not achieve significance. In contrast, in patients with liver cirrhosis renal vascular resistance increased by ~20% (66.6 ± 4.7 *vs* 79.7 ± 8.5 mmHg · min/l; $P < 0.05$).

During EECP, the state of neuroendocrine activation changed: plasma ANP concentrations increased in

controls from 11.4 ± 4.3 to 16.2 ± 5.3 ng/l ($P < 0.01$) and cirrhotic patients alike from 22.6 ± 17.9 to 30.2 ± 20.5 ng/l ($P < 0.05$). Plasma renin concentration dropped in response to EECP: from 4.6 ± 1.6 to 3.4 ± 1.1 ng/l ($P < 0.01$; −26%) in the controls and from 97.6 ± 97.8 to 57.8 ± 57.2 ng/l ($P < 0.01$; −41%) in the cirrhotic patients. The very high renin concentrations of the cirrhotic patients may not have been attributable to cirrhosis alone. Most of the cirrhotics had been receiving diuretics as part of their treatment before. In fact, the diuretic prescription in the 19 cirrhotic patients had consisted of loop diuretics alone (eight patients) or in combination with spironolactone (11 patients). Also, it had not been possible to discontinue the diuretics for ≥12 h before EECP on clinical grounds.

In healthy controls, endothelin-1 levels fell during EECP. In contrast, plasma concentrations of endothelin-1 remained unchanged in the cirrhotic patients. Plasma concentrations of epinephrine and *N*-epinephrine exhibited no change during EECP in both groups.

Table 3 provides a breakdown of the data of Table 2 according to Child–Pugh class. According to Table 3, the changes at baseline in cirrhotic patients became more marked with increasing Child–Pugh class. The effects of EECP, when expressed as percentage change form baseline, were, however, comparably demonstrable in all three classes of the Child–Pugh classification.

The urine excretion rate increased from 3.2 ± 1.9 to 4.6 ± 1.9 ml/min ($P < 0.05$) in healthy volunteers and from 1.8 ± 1.5 to 2.8 ± 1.9 ml/min ($P < 0.05$) in cirrhotic patients. Sodium and chloride excretion rates also rose in both groups (Table 2).

Although plasma ADH failed to change significantly in either group (Table 2), urinary osmolality decreased from 487 ± 280 to 274 ± 69 mosm/kg H_2O in controls (−40%; $P < 0.05$) and from 516 ± 240 to 405 ± 248 mosm/kg H_2O in patients (−20%; $P < 0.05$).

Discussion

To the best of our knowledge EECP has not been described in patients with liver cirrhosis before. We deduced that EECP in liver cirrhosis might have effects similar to previously described head-out water immersion. In the present study we made three observations: (a) EECP is feasible in cirrhotic patients; (b) EECP is effective and produces significant improvements of mean arterial pressure and renal excretion of salt and water; and (c) in cirrhosis, EECP induced a paradoxical increase of renal vascular resistance in response to an increased perfusion pressure. This has not been shown before. With respect to our findings we would like to offer the following comments.

We did not perform a direct comparison between EECP and water immersion. However, EECP was obviously well tolerated by the patients and easy to perform for the investigators. Throughout the procedure the patients rested supine. They did not have to change dress or environment nor was it necessary to keep the experimental set-up strictly thermoneutral, as in water immersion. There were no medical complications. In particular, there was no damage to the skin or the legs. It was our impression that EECP could easily be repeated on successive days if it was to be used for therapeutic purposes.

The cirrhotic patients observed in our study were in three different classes of severity according to the Child–Pugh classification. Only 10 out of 19 cirrhotic patients had ascites (Table 1). All patients had characteristic abnormalities of cirrhosis (Table 2): their mean arterial pressure was reduced, the renal excretion rates of sodium and chloride as well as urine flow were lower than in controls, while plasma

Table 3. Effects of EECP on parameters of cardiovascular and renal function and on plasma parameters in patients with liver cirrhosis according to Child–Pugh class

	Child–Pugh A ($n = 6$)		Child–Pugh B ($n = 9$)		Child–Pugh C ($n = 4$)	
	Before EECP	2 h of EECP	Before EECP	2 h of EECP	Before EECP	2 h of EECP
Urinary excretion rate (ml/min)	3.2 ± 1.9	4.6 ± 1.9	1.2 ± 0.8	1.6 ± 1.0[a]	1.2 ± 0.4	2.9 ± 1.6
Urinary sodium excretion rate (mmol/min)	0.22 ± 0.13	0.35 ± 0.17[a]	0.08 ± 0.05	0.13 ± 0.07[b]	0.05 ± 0.05	0.07 ± 0.06
Urinary chloride excretion rate (mmol/min)	0.16 ± 0.13	0.25 ± 0.15	0.02 ± 0.02	0.05 ± 0.04[b]	0.02 ± 0.01	0.03 ± 0.03
Renal plasma flow (ml/min)	467 ± 88	512 ± 236	429 ± 157	516 ± 262	384 ± 154	383 ± 164
GFR (ml/min/1.73 m^2)	78 ± 24	73 ± 38	69 ± 35	76 ± 50	61 ± 49	56 ± 28
Urinary osmolality (mosm/kg H_2O)	387 ± 217	263 ± 101	639 ± 264	588 ± 241[a]	490 ± 68	263 ± 231
Mean arterial pressure (mmHg)	78.0 ± 30.1	87.1 ± 36.6[a]	67.9 ± 10.6	81.9 ± 11.8[a]	71.5 ± 13.1	85.5 ± 13.2
Renal vascular resistance (mmHg · min/l)	66.3 ± 26.3	85.4 ± 54.1	63.9 ± 20.8	71.2 ± 30.4	72.8 ± 14.0	90.0 ± 22.9
Plasma renin concentration (ng/l)	41 ± 44	28 ± 29	113 ± 118	72 ± 68	150 ± 87	75 ± 22
Plasma ANP concentration (ng/l)	17 ± 3.5	21 ± 3.5[a]	20.3 ± 4.1	26.5 ± 4.4[b]	36.1 ± 16.5	52.4 ± 16.3
Plasma endothelin-1 concentration (pmol/l)	1.83 ± 0.2	2.19 ± 0.1[a]	2.08 ± 0.10	2.22 ± 0.14	2.90 ± 0.37	2.71 ± 0.15
Plasma ADH concentration (ng/l)	2.9 ± 1.8	3.1 ± 1.7	11.0 ± 16.9	5.3 ± 3.7	19.9 ± 29.4	19.4 ± 28.7
Plasma epinephrine concentration (nmol/l)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.4	0.4 ± 0.2	0.6 ± 0.3	0.6 ± 0.4
Plasma norepinephrine concentration (nmol/l)	2.1 ± 1.6	1.9 ± 0.9	3.0 ± 1.5	2.8 ± 1.4	4.0 ± 2.0	4.1 ± 0.9

[a] $P < 0.05$; [b] $P < 0.01$ (for comparison between baseline and EECP).

N-epinephrine, epinephrine, renin, vasopressin and endothelin-1 were all increased. When we broke down the data (Table 2) according to the Child–Pugh classification (Table 3), it was found that the alterations became progressively more severe from Child A to C, as expected. Many patients were on diuretics and the daily dosages of spironolactone and furosemide were also different between the three groups. The withdrawal of the different doses of diuretics shortly before the study might also have affected the observations of urinary sodium excretion rate in the three Child classes.

In our study, EECP effectively increased arterial filling in cirrhosis. This was demonstrated in several ways: (A) by the enhancement of diastolic blood flow in the renal artery (Figure 3); (B) by the diastolic augmentation of the pulse wave curve (Figure 4); and (C) by the rise of measured mean arterial pressure in cirrhotic patients (Table 2). There was also an increase of ANP in cirrhotic patients and controls. In a previous study of EECP in patients with acute myocardial infarction [7] it was observed that EECP increased right atrial pressure. The effect was attributed to an increased venous return from the legs. Comparable changes may explain the increased ANP in the present study.

In the setting of an improved arterial filling, EECP augmented renal excretory function in cirrhosis. Similar data have been reported previously for water immersion [12,13]. Nicholls *et al.* [12,13] observed an increase of sodium excretion and suppression of renin, aldosterone, *N*-epinephrine and epinephrine in response to water immersion. Our present observations resembled this pattern of changes. Therefore, the results of both manoeuvres, water immersion and EECP, are compatible with the 'underfilling hypothesis' of the arterial circulation in cirrhosis [12,13]. We would like to indicate that this effectiveness of EECP may be useful in terms of practical application. For instance, it may be possible to use EECP in cirrhotics with excretory failure to determine the degree of reversibility of the failure. Also, repeated use of EECP to treat patients with cirrhosis and renal dysfunction might cause fewer side effects than the use of potent diuretics. While those aspects remain to be tested in the future, we feel that EECP is a feasible new technique for such purposes.

In previous work using water immersion in cirrhotic patients [14] it was noted that systemic vascular resistance (SVR) decreased as did mean arterial pressure. In the present study using EECP we did not measure SVR; however, we observed that renal vascular resistance also tended to fall in controls. In contrast, it rose significantly and by ~20% in cirrhotic patients. We consider this paradoxical increase a major new observation generated by the present study. Although it was known before that renal vessels are relatively constricted whereas mesenteric vessels are vasodilated in cirrhosis [1,14], it has not been demonstrated before that renal vasculature in cirrhosis fails to dilate in response to an increased perfusion pressure.

When flow is increased in an arterial blood vessel in response to an increased perfusion pressure most vessels respond by vasodilation [15]. Increased flow causes increased shear stress to the vascular endothelium. This in turn stimulates generation of several vascular mediators, such as nitric oxide, reactive oxygen species and prostaglandin E_2, whereas endothelin-1 is downregulated [16,17]. Shear stress is the most important physiological stimulus in the release of nitric oxide from endothelial cells [16] and nitric oxide is known as a very potent vasodilator. The shear stress regulation of endothelial nitric oxide synthase sets in rapidly and increases nitric oxide generation over ~60 min, after which a plateau phase of sustained increase of nitric oxide is maintained [18]. A previous study demonstrated an increase of nitric oxide during the EECP manoeuvre [19]. Nitric oxide levels increased by 18% on average in patients with coronary artery disease after 1 h of EECP.

In the present work, an EECP-induced vasodilation was observed in the renal vasculature of normal controls since renal vascular resistance fell. It is possible that this vasodilation was related, in part, to alterations of measured neuroendocrine and paracrine mediators, such as the decrease of renin and endothelin-1 and the increase of ANP in controls. We cannot exclude any effects via the hepatorenal reflex mechanism, since we did not measure renal sympathetic nerve activity. However, since other important mediators, such as *N*-epinephrine, epinephrine and vasopressin, remained unchanged or tended to increase we reasoned that these changes on balance may not suffice to explain the increase of renal plasma flow in controls. Hence, shear stress-induced arterial vasodilation may provide the primary explanation. In cirrhotic patients the pattern of neuroendocrine and paracrine changes resembled those in normal controls; in particular, none of the measured vasoconstrictors increased. Yet, renal vascular resistance showed a major rise from 67 ± 5 to 79 ± 8 mmHg · min/l. We cannot exclude that an unmeasured or unknown element of vasoconstriction was responsible for these changes. However, present evidence would suggest that renal vasculature of cirrhotic patients fails to show a normal intrinsic response to shear stress. It is interesting in this respect that a recent report was able to describe a significant improvement of renal function in liver cirrhosis and hepatorenal syndrome following the use of *N*-acetylcysteine, an antioxidant [20], since increased oxidative stress is known to cause endothelial dysfunction, including a defective response of shear stress. However, the present work had not been planned to measure potential mechanisms of a deficient shear stress response in renal vessels in cirrhosis.

To conclude, in this pilot study we could demonstrate that EECP is a safe and feasible procedure in patients with liver cirrhosis. Short-term EECP yielded an increase in diuresis and natriuresis in cirrhotic patients. The pathological renal vasoconstriction in patients with liver cirrhosis, however, could not be normalized by this procedure.

Conflict of interest statement. Dr D Welner MD received an unrestricted research fund from Vasomedical Inc, Westburg, New York, USA. All other authors have declared no conflict of interest.

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