

Effect of meal induced splanchnic arterial vasodilatation on renal arterial haemodynamics in normal subjects and patients with cirrhosis

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Abstract

Aims—To investigate the relation between changes in splanchnic arterial haemodynamics and renal arterial haemodynamics in controls and patients with cirrhosis.

Methods—Superior mesenteric artery pulsatility index (SMA-PI) and renal artery pulsatility index (R-PI) were measured using Doppler ultrasonography in 24 controls and 36 patients with cirrhosis. These measurements were repeated 30 minutes after ingestion of a liquid meal or placebo. Sixteen controls and 24 patients received the meal, and eight controls and 12 patients received placebo.

Results—In the fasting condition, patients with cirrhosis had a lower SMA-PI ($p < 0.01$) and a greater R-PI ($p < 0.01$) compared with controls. Placebo ingestion had no effect on splanchnic and renal haemodynamics. In contrast, ingestion of the meal caused a notable reduction in SMA-PI ($p < 0.01$, $p < 0.01$) and an increase in R-PI ($p < 0.01$, $p < 0.01$) in controls and patients with cirrhosis. The meal induced haemodynamic change in SMA-PI was inversely correlated with that in R-PI in controls ($t = -0.42$, $p < 0.05$) and in patients with cirrhosis ($t = -0.29$, $p < 0.05$).

Conclusions—Results support the hypothesis that renal arterial vasoconstriction seen in patients with cirrhosis is one of the kidney's homeostatic responses to underfilling of the splanchnic arterial circulation.

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Keywords: cirrhosis; Doppler ultrasonography; pulsatility index; renal artery; superior mesenteric artery

Hyperdynamic circulation, characterised by increased cardiac output, normal or low arterial pressure, and decreased peripheral vascular resistance, has long been recognised in patients with cirrhosis.¹⁻⁴ According to a recently proposed hypothesis, peripheral arterial vasodilatation plays an important role in the initiation of hyperdynamic circulation.⁵ There is much evidence to show that the arterial vasodilatation occurs mainly in the splanchnic vascular bed in patients with cirrhosis.^{6,7} In contrast, the opposite haemodynamic status has been reported in the kidney. For example, decreased renal perfusion⁸⁻¹⁰ and increased renal arterial vascular tone¹¹ have

been described in patients with cirrhosis. Such renal arterial vasoconstriction might be explained as being one of the kidney's homeostatic responses to underfilling of the splanchnic arterial circulation.⁵ If this interpretation is correct, renal arterial vasoconstriction should occur in response to splanchnic arterial vasodilatation. However, no one has tried to test this hypothesis.

The aim of this study was therefore to investigate the relation between changes in splanchnic arterial haemodynamics and renal arterial haemodynamics in controls and patients with cirrhosis. For this purpose, we measured fasting and postprandial splanchnic and renal arterial vascular tones because it has been shown that ingestion of a meal causes selective splanchnic arterial vasodilatation.^{12,13}

Materials and methods

STUDY POPULATION

Thirty normal subjects served as controls and 45 patients with cirrhosis were initially considered for the study. However, six normal controls and nine patients with cirrhosis were excluded because of unsatisfactory sonographic visualisation of the superior mesenteric artery ($n = 11$), unsatisfactory Doppler signal from the kidney ($n = 2$), or poor cooperation of the subject ($n = 2$). Thus, only 24 controls and 36 patients with cirrhosis were finally enrolled.

The diagnosis of cirrhosis was based on liver biopsy or on clinical grounds. The cause of cirrhosis was posthepatic cirrhosis due to hepatitis B virus infection in five patients, hepatitis C virus infection in 29, and alcoholic in two. According to the Pugh-Child classification,¹⁴ 14 patients had grade A disease, 16 grade B disease, and six grade C disease. Eight patients had ascites or oedema on clinical and ultrasonographic examination at the time of study. Twenty four patients had endoscopy visualised oesophagogastric varices, and six had a previous history of endoscopic variceal obliteration. Twelve patients received diuretics, but the drugs were stopped at least three days before the investigation. Informed consent was obtained from each patient and the study protocol conformed to the requirements of the 1975 Declaration of Helsinki.

STUDY PROTOCOL

All subjects were studied in the morning after an overnight fast. After 30 minutes of bed rest, baseline Doppler measurements were performed with the subject in a supine position in

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Table 1 Haemodynamic data of controls and patients with cirrhosis

Parameter	Controls (n=24)	Patients (n=36)
Mean arterial pressure (mm Hg)	88.3 (2.1)	87.5 (1.4)
Heart rate (beats/min)	61.0 (1.5)	65.4 (1.6)*
Cardiac index (l/min/m ²)	2.26 (0.12)	3.00 (0.11)**
Peripheral vascular resistance index (dyn/sec/cm ⁵ /m ²)	3330 (198)	2461 (109)**
Superior mesenteric artery pulsatility index	3.07 (0.08)	2.41 (0.06)**
Renal artery pulsatility index	0.96 (0.03)	1.12 (0.04)**

*p<0.05, **p<0.01 v controls.

order to obtain cardiac output and haemodynamic parameters of the superior mesenteric artery and intrarenal artery. Heart rate and mean arterial pressure [(systolic pressure + diastolic pressure × 2)/3] were also recorded with the subject in a supine position. Subjects were then randomised to receive a standardised mixed liquid meal or placebo meal. The meal (1.05 MJ, Ensure Liquid, Dainabot, Osaka, Japan) was composed of 8.3 g proteins, 8.3 g fat, 34.3 g carbohydrates, and 213 ml of water. The energy distribution was as follows: 14% from protein, 31.5% from fat, and 54.5% from carbohydrates. The placebo meal was an equivalent volume of water (250 ml). The randomisation sequence was biased to place more subjects in the meal than in the placebo group (ratio 2:1). Thus, 16 in the control group and 24 in the patient group received the meal, and eight in the control group and 12 in the patient group received placebo. The measurements were repeated 30 minutes after ingestion of the meal or placebo. All Doppler measurements were performed by one of the authors (TI). The operator did not know the characteristics of the subjects nor whether they received the meal or placebo.

DOPPLER MEASUREMENTS AND CALCULATIONS

We used a duplex Doppler apparatus (EUB-555, Hitachi, Tokyo, Japan) with 2.5 MHz and 7.5 MHz transducers for heart, superior mesenteric artery, and kidney. A cut off filter of 100 Hz was installed to eliminate possible artifacts from vessel wall motion. Real time and Doppler settings were optimised in each case.

Cardiac output (l/min) was measured according to the left ventricular outflow method.¹⁵ In brief, the sample volume was placed in the middle of the left ventricular outflow immediately proximal to the leaflet of the aortic valve in the apical five chamber view and the time-velocity integral was obtained by Doppler traces of one cardiac cycle. The aortic annulus diameter was measured in the parasternal long axis view and the cross sectional area of the aortic annulus was calculated as $\pi \times D^2$, where D represents half of the aortic annulus diameter. Stroke volume was calculated by the product of the time-velocity integral and the cross sectional area of the ascending aorta. Cardiac output was then calculated from the product of stroke volume and heart rate and expressed as the cardiac index (l/min/m²). Peripheral vascular resistance index (dyn/sec/cm⁵/m²) was calculated as follows: peripheral vascular resistance index = mean arterial pressure × 80/cardiac index.

To measure superior mesenteric artery pulsatility index, the superior mesenteric artery

was scanned longitudinally. The sample volume cursor was then shifted to the distal straight part of superior mesenteric artery (3–5 cm from the origin), and the Doppler beam was discharged. To obtain a satisfactory Doppler signal, the transducer position was determined by maximising the power return waveforms.¹⁶ In this situation, the velocity waveform must be smooth and peaked whereas the power return waveforms must have maximal amplitude and a peak that is flat or slightly downsloping.¹⁶ Peak systolic, end diastolic, and temporal mean flow velocity were then determined, and from them the pulsatility index was calculated according to the following formula¹⁷: pulsatility index = (peak systolic velocity – end diastolic velocity)/mean velocity.

With regard to the kidney examination, colour Doppler imaging was used to access easily the intrarenal arteries, such as the interlobar, interlobular, or arcuate arteries. The sample volume cursor was shifted to an intrarenal artery and the blood flow velocity waveform was recorded. Renal artery pulsatility index was then calculated by the above mentioned formula.

In this study, five consecutive measurements were made for heart, superior mesenteric artery, and renal artery, and the average value was used for data analysis. Our previous study has shown intraobserver (TI) coefficients of variation for cardiac output and superior mesenteric artery pulsatility index to be 11%, and 6%, respectively.⁷ To evaluate intraobserver (TI) reproducibility of renal artery pulsatility index, duplicate measurements separated by 30 minutes were performed in 12 subjects. The coefficient of variation was 4%.

DATA ANALYSIS

Results are reported as mean (SE). Differences between the two groups in clinical and haemodynamic variables were compared by the Mann-Whitney U test for continuous data and χ^2 test for categorical data. The effect of the meal and placebo on haemodynamic variables was evaluated by the Wilcoxon signed rank test for paired samples. The interaction between the two haemodynamic variables was examined using Kendall rank correlation analysis. All data analyses were performed using the computer software StatView (Abacus Concepts, Inc., USA). Significance was established at p<0.05.

Results

BASELINE DATA

The control group consisted of 17 men and seven women with a mean age of 62 (2) years. The patient group consisted of 24 men and 12 women with a mean age of 61 (1) years. There were no significant differences in age and sex between the two groups.

In systemic haemodynamics, mean arterial pressure was similar in controls and patients with cirrhosis. However, cardiac index was significantly higher in patients with cirrhosis than in controls (p<0.01). Therefore, the peripheral vascular resistance index was significantly lower in patients with cirrhosis than in controls

Table 2 Effect of placebo on haemodynamic data of controls and patients with cirrhosis

Parameter	Controls (n=8)		Patients (n=12)	
	Baseline	After meal	Baseline	After meal
Mean arterial pressure (mm Hg)	87.2 (4.2)	86.0 (4.7)	85.0 (2.5)	84.9 (2.7)
Heart rate (beats/min)	61.3 (2.1)	60.6 (2.0)	66.2 (1.5)	65.7 (1.7)
Cardiac index (l/min/m ²)	2.18 (0.17)	2.24 (0.21)	3.26 (0.24)	3.18 (0.23)
Peripheral vascular resistance index (dyn/sec/cm ⁵ /m ²)	3386 (365)	3299 (416)	2247 (210)	2274 (192)
Superior mesenteric artery pulsatility index	3.15 (0.13)	3.14 (0.11)	2.34 (0.10)	2.32 (0.08)
Renal artery pulsatility index	1.01 (0.04)	1.01 (0.05)	1.16 (0.05)	1.16 (0.04)

Table 3 Effect of the meal on haemodynamic data of controls and patients with cirrhosis

Parameter	Controls (n=16)		Patients (n=24)	
	Baseline	After meal	Baseline	After meal
Mean arterial pressure (mm Hg)	88.9 (2.5)	84.3 (2.7)	88.7 (1.7)	85.1 (1.5)
Heart rate (beats/min)	60.9 (2.0)	64.7 (1.7)**	65.0 (1.5)	67.5 (1.7)**
Cardiac index (l/min/m ²)	2.30 (0.16)	2.55 (0.16)**	2.89 (0.14)	3.03 (0.13)**
Peripheral vascular resistance index (dyn/sec/cm ⁵ /m ²)	3302 (243)	2805 (201)**	2569 (122)	2352 (114)**
Superior mesenteric artery pulsatility index	3.02 (0.10)	2.05 (0.07)**	2.44 (0.07)	1.82 (0.04)**
Renal artery pulsatility index	0.93 (0.03)	1.08 (0.05)**	1.10 (0.05)	1.15 (0.04)**

**p<0.01 v baseline.

(p<0.01). Heart rate was significantly higher in patients with cirrhosis than in controls (p<0.05). In regional haemodynamics, superior mesenteric artery pulsatility index was significantly lower in patients with cirrhosis than in controls (p<0.01) whereas renal artery pulsatility index was significantly higher in patients with cirrhosis than in controls (p<0.01) (table 1).

EFFECT OF PLACEBO INGESTION ON SYSTEMIC AND REGIONAL HAEMODYNAMICS

Placebo ingestion had no significant effect on systemic and regional haemodynamics in either controls or patients with cirrhosis (table 2).

EFFECT OF MEAL INGESTION ON SYSTEMIC AND REGIONAL HAEMODYNAMICS

Meal ingestion induced a similar haemodynamic change in the two groups. Although meal ingestion caused no significant change in mean arterial pressure, it increased cardiac index (controls, p<0.01; patients with cirrhosis, p<0.01). Thus, the peripheral vascular resistance index was significantly decreased after ingestion of the meal (p<0.01, p<0.01). Meal ingestion also increased heart rate (p<0.01, p<0.01). With respect to regional haemodynamics, meal ingestion caused a significant reduction in superior mesenteric artery pulsatility index (p<0.01, p<0.01) but a significant increase in renal artery pulsatility index (p<0.01, p<0.01) (table 3).

Patients with cirrhosis had a blunted postprandial haemodynamic responsiveness in relation to cardiac index (5 (2)% versus 12 (2)%, p<0.05), superior mesenteric artery pulsatility index (-25 (2)% versus -32 (2)%, p<0.05), and renal artery pulsatility index (6 (1)% versus 16 (2)%, p<0.05). When the ratio of the meal induced haemodynamic change in cardiac index and renal artery pulsatility index to that in superior mesenteric artery pulsatility index was further calculated, the ratio of percentage change in cardiac index to that in superior mesenteric artery pulsatility index was still significantly lower in patients with cirrhosis than in controls (0.21 (0.08) versus 0.35 (0.07), p<0.05). Similarly, the ratio of percentage change in renal artery pulsatility index to that in superior mesenteric artery pulsatility index was also significantly lower in patients with cirrhosis than in controls (0.22 (0.04) versus 0.51 (0.05), p<0.01).

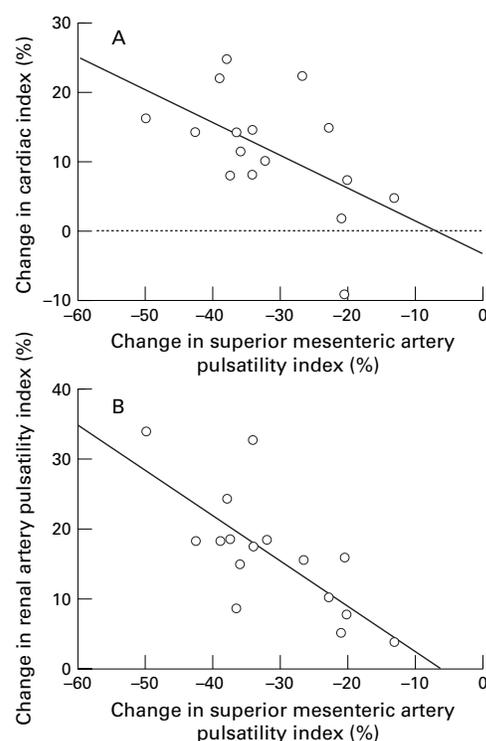


Figure 1 Correlation between the meal induced haemodynamic change in (A) superior mesenteric artery pulsatility index and cardiac index ($r=-0.42$, $p<0.05$), and (B) renal artery pulsatility index ($r=-0.42$, $p<0.05$) in controls.

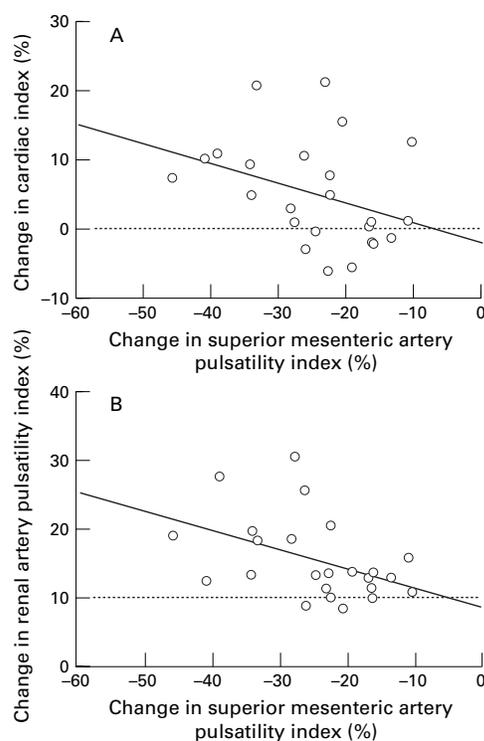


Figure 2 Correlation between the meal induced haemodynamic change in (A) superior mesenteric artery pulsatility index and cardiac index ($t=-0.24$, $p=0.10$), and (B) renal artery pulsatility index ($t=-0.29$, $p<0.05$) in patients with cirrhosis.

CORRELATIONS

Under baseline conditions, superior mesenteric artery pulsatility index did not correlate with peripheral vascular resistance index ($t=0.07$, $p=0.72$). In contrast, in patients with cirrhosis, there was a direct relation between superior mesenteric artery pulsatility index and peripheral vascular resistance index ($t=0.30$, $p<0.05$). The relations between superior mesenteric artery pulsatility index and renal artery pulsatility were not significant in controls ($t=-0.10$, $p=0.60$) and patients with cirrhosis ($t=-0.15$, $p=0.30$).

The meal induced haemodynamic change in superior mesenteric artery pulsatility index was inversely correlated with that of both cardiac index ($t=-0.42$, $p<0.05$) and renal artery pulsatility index ($t=-0.42$, $p<0.05$) in controls (fig 1). In patients with cirrhosis, similar findings were observed but the correlations were somewhat weak (change in superior mesenteric artery pulsatility index versus that in cardiac index: $t=-0.24$, $p=0.10$; change in superior mesenteric artery pulsatility index versus that in renal artery pulsatility index: $t=-0.29$, $p<0.05$) (fig 2).

Discussion

The goal of this study was to determine whether renal arterial vasoconstriction occurs in response to splanchnic arterial vasodilatation in humans. To obtain haemodynamic data in each vascular bed, we examined the superior mesenteric artery and intrarenal artery using Doppler ultrasonography. However, it has been stressed that the Doppler technique is subject

to many possible errors.¹⁷ Therefore, this study was undertaken in a strict observer blinded condition. Furthermore, we only used pulsatility index as a haemodynamic parameter of each vascular bed. The reasons were the following: (1) pulsatility index is a good indicator in the estimation of regional vascular tone¹⁸; (2) determination of pulsatility index is not affected by the angle between the direction of the Doppler beam and the blood vessel,¹⁹ resulting in a higher observer agreement in comparison with flow velocity and flow volume measurements; (3) pulsatility index might complement the information derived from the flow volume when the measurement of flow volume is either difficult or impossible¹⁹; and (4) interobserver variability of pulsatility index in various vascular beds is small.²⁰ Indeed, with regard to the intraobserver variability, the coefficient of variation was only 6% for the superior mesenteric artery pulsatility index and 4% for the renal artery pulsatility index. It should also be emphasised that the pulsatility index in each vessel in the fasting condition was very similar to that after placebo ingestion. Therefore, the reliability of the current Doppler study seems to be acceptable.

In agreement with previous studies,¹⁻⁴ our patients with cirrhosis had hyperdynamic circulation, characterised by increased cardiac index and decreased peripheral vascular resistance index. In splanchnic haemodynamics, we were previously able to show that the superior mesenteric artery pulsatility index was significantly lower in patients with cirrhosis than in controls.⁷ In renal haemodynamics, Sacerdoti *et al*¹¹ have shown that the renal artery pulsatility index was significantly higher in patients with cirrhosis than in controls. In this study, we confirmed these findings. Therefore, regional haemodynamics in patients with cirrhosis are characterised by a decreased splanchnic arterial vascular tone associated with an increased renal arterial vascular tone.

When superior mesenteric artery pulsatility index correlated with peripheral vascular resistance index and renal artery pulsatility index, no significant relations were observed in controls. In contrast, in accordance with our previous series,⁷ there was a direct relation between superior mesenteric artery pulsatility index and peripheral vascular resistance index in patients with cirrhosis. This suggests that the site of arterial vasodilatation in patients with cirrhosis occurs mainly in the splanchnic arterial circulation.

Meal ingestion is a powerful splanchnic arterial vasodilator in humans.¹² In this study, we found that meal ingestion caused a notable reduction in the superior mesenteric artery pulsatility index in both controls and patients with cirrhosis. However, the reduction was less pronounced in patients with cirrhosis. This may be explained by the fact that the already dilated splanchnic vascular bed in patients with cirrhosis cannot dilate as much as that of normal subjects.

Previous studies in healthy humans have shown that meal ingestion increases cardiac output.²⁰⁻²¹ Similarly, a postprandial increase in

cardiac index was observed in our controls. Such a cardiac performance after meal ingestion is now thought to reflect compensatory cardiovascular and neurohumoral mechanisms, such as baroreflex mediated cardioacceleration and sympathetic nervous activation, in response to a systemic hypotensive stress induced by splanchnic blood pooling after the meal.²²⁻²⁴ In our controls, ingestion of the meal also caused renal arterial vasoconstriction. Indeed, a significant increase in the renal arterial pulsatility index was noted. Furthermore, we found significant inverse relations between the meal induced haemodynamic change in the superior mesenteric artery pulsatility index and either that in the cardiac index or that in the renal artery pulsatility index. These findings suggest that both increased cardiac contractility and renal arterial vasoconstriction seem to be important homeostatic responses to prevent hypotension due to postprandial splanchnic arterial vasodilatation. Indeed, arterial pressure homeostasis was almost intact during the study.

In our patients with cirrhosis, similar postprandial haemodynamic changes in systemic and renal haemodynamics were noted. For example, both the cardiac index and the renal artery pulsatility index increased significantly after ingestion of the meal. Although these haemodynamic changes were less pronounced in patients with cirrhosis than in controls, it should be noted that the magnitude of postprandial splanchnic arterial vasodilatation was also smaller in patients with cirrhosis than in controls. We thus calculated the ratio of the meal induced haemodynamic change in the cardiac index and the renal artery pulsatility index to that in the superior mesenteric artery pulsatility index. However, these values were still significantly lower in patients with cirrhosis than in controls. Thus, postprandial haemodynamic responsiveness of the heart and kidney seems to be reduced in patients with cirrhosis.

There are a number of possible explanations for this finding. Many authors found that ventricular responsiveness to physiological²⁵⁻²⁷ and pharmacological²⁸ stimuli is blunted in patients with cirrhosis, a phenomenon that has been termed cirrhotic cardiomyopathy. Thus, reduced postprandial cardiac responsiveness observed in our patients with cirrhosis is not surprising. Recent experimental studies²⁹⁻³⁰ have shown that the β adrenoceptor and its signal transduction pathway play a critical role in the pathogenesis of cirrhotic cardiomyopathy. The reason for the decreased renal arterial responsiveness observed in patients with cirrhosis is not clear. However, it may be speculated that the already contracted renal arterial vascular bed in these patients cannot contract as much as that of normal subjects. Another possible explanation is downregulation or desensitisation of the vasoconstrictive influence. This may be supported by the previous studies in which both endogenous and exogenous sympathoadrenergic activations show depressed vascular responsiveness in patients with cirrhosis.³¹⁻³²

In our patients with cirrhosis, despite blunted postprandial haemodynamic responsiveness of the heart and the kidney, arterial pressure homeostasis was preserved. Interestingly, a recent study from our laboratory⁷ has shown that femoral artery vascular tone tends to increase in patients with advanced cirrhosis in comparison to those in the early stage of the disease. This suggests that femoral arterial vasoconstriction, as well as renal arterial vasoconstriction, also plays an important role in the maintenance of arterial pressure homeostasis in patients with severe cirrhosis. Therefore, the potential role of extrarenal arterial vasoconstriction in the maintenance of postprandial arterial pressure homeostasis in patients with cirrhosis cannot be ruled out. This might be further supported by the current results in which no significant inverse relation between the superior mesenteric artery pulsatility index and the renal artery pulsatility index was detected in the patients with cirrhosis in the fasting condition.

It has been shown that renal arterial vasoconstriction plays an important role in the development of the hepatorenal syndrome in patients with cirrhosis.⁵⁻¹¹ Thus, a rational therapeutic approach to the hepatorenal syndrome is believed to be to reverse the renal arterial vasoconstriction. Our results showing an inverse interaction between renal and splanchnic arterial vascular tone may support the potential usefulness of a splanchnic arterial vasoconstrictor in the treatment of the hepatorenal syndrome. Interestingly, Lenz and colleagues³³ have shown that administration of ornipressin induces an increase in peripheral vascular resistance associated with a decrease in renal vascular resistance and an increase in renal perfusion. It should be noted that intrarenal or intravenous administration of vasodilators or drugs that inhibit the synthesis or the effect of endogenous vasoconstrictors have failed to improve renal function.³⁴

In conclusion, the present study shows that renal arterial vascular tone is inversely regulated by splanchnic arterial vascular tone in humans. This finding may support the hypothesis that the renal arterial vasoconstriction seen in patients with cirrhosis is one of the kidney's homeostatic responses to underfilling of the splanchnic arterial circulation. Future studies looking at the renal response to another non-pharmacological blood pooling stimulus such as lower body negative pressures are needed to confirm this hypothesis.

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- 1 Kowalski HJ, Abelmann WH. Cardiac output at rest in Laennec's cirrhosis. *J Clin Invest* 1953;32:1025-33.
- 2 Murray JF, Dawson AM, Sherlock S. Circulatory changes in chronic liver disease. *Am J Med* 1958;24:358-67.
- 3 Kontos HA, Shapiro W, Mauck HP, et al. General and regional circulatory alterations in cirrhosis of the liver. *Am J Med* 1964;37:526-35.
- 4 Liberman FL, Reynolds TB. Plasma volume in cirrhosis of the liver. Its relation to portal hypertension, ascites and renal failure. *J Clin Invest* 1967;46:1297-308.
- 5 Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151-7.

- 6 Maroto A, Ginès P, Arroyo V, et al. Brachial and femoral artery blood flow in cirrhosis: relationship to kidney function. *Hepatology* 1993;17:788-93.
- 7 Iwao T, Oho K, Sakai T, et al. Splanchnic and extrasplanchnic arterial hemodynamics in patients with cirrhosis. *J Hepatol* 1997;27:817-23.
- 8 Kew NC, Varma RR, Williams HS, et al. Renal and intrarenal blood flow in cirrhosis of the liver. *Lancet* 1971;49:504-10.
- 9 Moreau R, Gaudin C, Hadengue A, et al. Renal hemodynamics in patients with cirrhosis: relationship with ascites and liver failure. *Nephron* 1993;65:359-63.
- 10 Fernandez-Seara J, Prieto J, Quiroga J, et al. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. *Gastroenterology* 1989;97:1304-12.
- 11 Sacerdoti D, Bolognesi M, Merkel C, et al. Renal vasoconstriction in cirrhosis evaluated by Duplex Doppler ultrasonography. *Hepatology* 1993;17:219-24.
- 12 Sabbá C, Eerraioli G, Genecin P, et al. Evaluation of postprandial hyperemia in superior mesenteric artery and portal vein in healthy and cirrhotic humans: an operator-blind echo-Doppler study. *Hepatology* 1991;13:714-8.
- 13 Iwao T, Toyonaga A, Oho K, et al. Postprandial splanchnic hemodynamic response in patients with cirrhosis of the liver: evaluation with "triple-vessel" duplex US. *Radiology* 1996;201:711-15.
- 14 Pugh RNH, Murray-Lyon M, Dawson JL, et al. Transsection of oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-9.
- 15 Lewis JF, Kuo LC, Nelson JG, et al. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 1984;70:425-31.
- 16 Looyenga DS, Liebson PR, Bone RC, et al. Determination of cardiac output in critically ill patients by dual beam Doppler echocardiography. *J Am Coll Cardiol* 1989;13:340-7.
- 17 Taylor KJW, Holland S. Doppler ultrasound. Part 1. Basic principles, instrumentation, and pitfalls. *Radiology* 1990;174:297-307.
- 18 McCallum WD, Williams CS, Napel S, et al. Fetal blood velocity waveform. *Am J Obstet Gynecol* 1978;132:425-9.
- 19 Qarmer MI, Read AE, Skidmore R, et al. Pulsatility index of superior mesenteric artery waveform. *Ultrasound Med Biol* 1986;12:773-6.
- 20 Sacerdoti D, Gaiani S, Buonamico P, et al. Interobserver and interequipment variability of hepatic, splenic, and renal arterial Doppler resistance indices in normal subjects and patients with cirrhosis. *J Hepatol* 1997;27:986-92.
- 21 Kelbaek H, Munck O, Christensen NJ, et al. Central haemodynamic changes after a meal. *Br Heart J* 1986;61:506-9.
- 22 Fagan TC, Sawyer PR, Gourley LA, et al. Postprandial alterations in hemodynamics and blood pressure in normal subjects. *Am J Cardiol* 1986;58:636-41.
- 23 Lipsitz LA, Nyquist RP Jr, Wei JY, et al. Postprandial reduction in blood pressure in the elderly. *N Engl J Med* 1983;309:81-3.
- 24 Lipsitz LA, Pluchino FC, Wei JY, et al. Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope. *Am J Cardiol* 1986;58:810-5.
- 25 Lee SS, Hadengue A, Moreau R, et al. Postprandial hemodynamic responses in patients with cirrhosis. *Hepatology* 1988;8:647-51.
- 26 Grose RD, Nolan J, Dillon JF, et al. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. *J Hepatol* 1995;22:326-32.
- 27 Bernardi M, Rubboli A, Trevisani F, et al. Reduced cardiovascular responsiveness to exercise-induced sympathoadrenergic stimulation in patients with cirrhosis. *J Hepatol* 1991;12:207-16.
- 28 Ramond MJ, Comoy E, Lebrec D. Alterations in isoprenaline sensitivity in patients with cirrhosis: evidence of abnormality of the sympathetic nervous activity. *Br J Clin Pharmacol* 1986;21:191-6.
- 29 Ma Z, Meddings JB, Lee SS. Membrane physical properties determine cardiac β -adrenergic receptor function in cirrhotic rats. *Am J Physiol* 1994;267:G87-93.
- 30 Ma Z, Miyamoto A, Lee SS. Role of altered β -adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. *Gastroenterology* 1996;110:1191-8.
- 31 Lunzer M, Newman SP, Sherlock S. Skeletal muscle blood flow and neurovascular reactivity in liver disease. *Gut* 1973;14:354-9.
- 32 Lunzer MR, Manghani KK, Newman SP, et al. Impaired cardiovascular responsiveness in liver disease. *Lancet* 1977;i:382-5.
- 33 Lenz K, Hörtnagl H, Druml W, et al. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. Effects on renal hemodynamics and atrial natriuretic factor. *Gastroenterology* 1991;101:1060-7.
- 34 Laffi G, La Villa G, Gentilini P. Pathogenesis and management of the hepatorenal syndrome. *Semin Liver Dis* 1994;14:71-81.