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

T Iwao, K Oho, R Nakano, M Yamawaki, T Sakai, M Sato, Y Miyamoto, A Toyonaga, K Tanikawa

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 (r=−0.42, p<0.05) and in patients with cirrhosis (r=−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.

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 posthepatitic 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...
Table 1  Haemodynamic data of controls and patients with cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=24)</th>
<th>Patients (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88.3 (2.1)</td>
<td>87.5 (1.4)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61.0 (1.5)</td>
<td>65.4 (1.6)*</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.26 (0.12)</td>
<td>3.00 (0.11)**</td>
</tr>
<tr>
<td>Peripheral vascular resistance index (dyn/sec/cm²/m²)</td>
<td>3330 (198)</td>
<td>2461 (109)**</td>
</tr>
<tr>
<td>Superior mesenteric artery pulsatility index</td>
<td>3.07 (0.08)</td>
<td>2.41 (0.06)**</td>
</tr>
<tr>
<td>Renal artery pulsatility index</td>
<td>0.96 (0.03)</td>
<td>1.12 (0.04)**</td>
</tr>
</tbody>
</table>

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

In 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. 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 π × D²/4, where D represents half of the aortic anulus 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/cm²/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. 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. Peak systolic, end diastolic, and temporal mean flow velocity were then determined, and from them the pulsatility index was calculated according to the following formula:

pulsatility index = (peak systolic velocity – end diastolic velocity)/mean velocity.

With regard to the kidney examination, our 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. To evaluate intraobserver (TT) 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 χ² 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.
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 post-prandial 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 (0.07) 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).

---

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=8)</th>
<th>Patients (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After meal</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>87.2 (4.2)</td>
<td>86.0 (4.7)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61.3 (2.1)</td>
<td>60.6 (2.0)</td>
</tr>
<tr>
<td>Cardiac index (/min/m²)</td>
<td>2.18 (0.17)</td>
<td>2.24 (0.21)</td>
</tr>
<tr>
<td>Peripheral vascular resistance index (dyn/sec/cm²/m²)</td>
<td>3386 (365)</td>
<td>3299 (416)</td>
</tr>
<tr>
<td>Superior mesenteric artery pulsatility index</td>
<td>3.15 (0.13)</td>
<td>3.14 (0.11)</td>
</tr>
<tr>
<td>Renal artery pulsatility index</td>
<td>1.01 (0.04)</td>
<td>1.01 (0.05)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=16)</th>
<th>Patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After meal</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88.9 (2.5)</td>
<td>84.3 (2.7)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60.9 (2.0)</td>
<td>64.7 (1.7)**</td>
</tr>
<tr>
<td>Cardiac index (/min/m²)</td>
<td>2.30 (0.16)</td>
<td>2.55 (0.16)**</td>
</tr>
<tr>
<td>Peripheral vascular resistance index (dyn/sec/cm²/m²)</td>
<td>3302 (243)</td>
<td>2805 (201)**</td>
</tr>
<tr>
<td>Superior mesenteric artery pulsatility index</td>
<td>3.02 (0.10)</td>
<td>2.05 (0.07)**</td>
</tr>
<tr>
<td>Renal artery pulsatility index</td>
<td>0.93 (0.03)</td>
<td>1.08 (0.05)**</td>
</tr>
</tbody>
</table>

**Figure 1**  Correlation between the meal induced haemodynamic change in (A) superior mesenteric artery pulsatility index and cardiac index (t=−0.42, p<0.05), and (B) renal artery pulsatility index (t=−0.42, p<0.05) in controls.
stressed that the Doppler technique is subject to many possible errors. 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 tone; (2) determination of pulsatility index is not affected by the angle between the direction of the Doppler beam and the blood vessel, 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 impossible; and (4) interobserver variability of pulsatility index in various vascular beds is small. 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, 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. In renal haemodynamics, Sacerdoti et al 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. The meal induced haemodynamic change in superior mesenteric artery pulsatility index was inversely correlated with that of both cardiac index ($r=-0.42$, $p<0.05$) and renal artery pulsatility index ($r=-0.42$, $p<0.05$) in patients with cirrhosis ($r=-0.10$, $p=0.60$) and patients with cirrhosis ($r=-0.15$, $p=0.30$).

The meal induced haemodynamic change in superior mesenteric artery pulsatility index was inversely correlated with that of both cardiac index ($r=-0.42$, $p<0.05$) and renal artery pulsatility index ($r=-0.42$, $p<0.05$) 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: $r=-0.24$, $p=0.10$; change in superior mesenteric artery pulsatility index versus that in renal artery pulsatility index: $r=-0.29$, $p<0.05$) (fig 2).

**CORRELATIONS**

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

**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
Renal and splanchnic arterial haemodynamics

have shown that the meal induced by splanchnic blood pooling after the meal. 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 homoeostasis 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 physiological and pharmacological 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 studies 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 sympathoadrenalergic activations show depressed vascular responsiveness in patients with cirrhosis.

In our patients with cirrhosis, despite blunted postprandial haemodynamic responsiveness of the heart and the kidney, arterial pressure homoeostasis was preserved. Interestingly, a recent study from our laboratory 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 homoeostasis in patients with severe cirrhosis. Therefore, the potential role of extrarenal arterial vasoconstriction in the maintenance of postprandial arterial pressure homoeostasis 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. 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 colleagues have shown that administration of orniressin 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.

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 homoeostatic 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.

This work was supported in part by Japanese Educational Ministry grant 08670636.

1 Kowalski HJ, Abelmamn WH. Cardiac output at rest in Laennec’s cirrhosis. J Clin Invest 1953;32:1025–33.


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

T Iwao, K Oho, R Nakano, M Yamawaki, T Sakai, M Sato, Y Miyamoto, A Toyonaga and K Tanikawa

Gut 1998 43: 843-848
doi: 10.1136/gut.43.6.843

Updated information and services can be found at:
http://gut.bmj.com/content/43/6/843

These include:

References
This article cites 33 articles, 4 of which you can access for free at:
http://gut.bmj.com/content/43/6/843#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/