Clinical Study

A Hemodynamic Study to Evaluate the Buffer Response in Cirrhotic Patients Undergoing Liver Transplantation

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The physiological regulation of the liver blood flow is a result of a reciprocal portal vein and hepatic artery flow relationship. This mechanism is defined as the hepatic arterial buffer response (HABR). This study was addressed to investigate whether HABR is maintained in denervated grafts in liver transplant recipients. Portal blood flow (PBF) and hepatic arterial resistance index (PI) were measured 6 months after transplantation using Doppler. In each patient we consecutively measured the vasodilator (Ensure Plus PO versus placebo) and vasoconstrictor (isosorbide dinitrate 5 mg SL versus placebo) stimuli. The meal ingestion caused a significant increase of both parameters, PBF (from 1495 ± 260 to 2069 ± 250 mL/min, \( P < 0.05 \)) and PI (from 0.7 ± 0.2 to 0.8 ± 0.2, \( P < 0.05 \)).

By contrast, isosorbide dinitrate reduced PBF (from 1660 ± 270 to 1397 ± 250 mL/min, \( P < 0.05 \)) and PI (from 0.7 ± 0.2 to 0.5 ± 0.2, \( P < 0.05 \)). We show that PBF and PI are reciprocally modified with the administration of vasoconstrictor and vasodilator stimuli. These results suggest the persistence of the HABR in a denervated human model, suggesting that this mechanism is independent of the regulation from the autonomic nervous system.

1. Introduction

Portal hypertension is associated with systemic hyperdynamic state characterized by a high cardiac output and a low peripheral vascular resistance [1]. The splanchnic circulation is also hyperkinetic, with an increase in portal blood flow, which is an important factor in the development and maintenance of the syndrome [2]. Recent studies have shown that restoration of normal hepatic function after liver transplantation should reverse hemodynamic disturbances [3–5].

During the last years, several experimental and clinical evidences have demonstrated reciprocity between changes in blood flow in the hepatic artery and the portal vein. It has been suggested that hepatic artery plays a passive role; that is, fluctuations in portal blood flow are buffered by inverse changes in arterial flow [6–8]. Until now, this physiological relationship has not been evaluated in stable liver transplant recipients. Therefore, the aims of the present study were (a) to evaluate hepatic arterial and portal blood flows after liver transplantation and (b) to measure the response of the hepatic artery to portal flow variations.

2. Material and Methods

2.1. Patients. Systemic and hepatic hemodynamic parameters were evaluated in eight patients with cirrhosis after six months of liver transplantation (ages 21 to 52 years). The cause of chronic liver disease was hepatitis C in 7 patients and cryptogenic in 1. Liver recipients were stable and none of them had clinical or histological evidence of infection or rejection. The patients received standard immunosuppression (tacrolimus or cyclosporine and prednisone). None of the patients were taking any form of vasoactive drug for the treatment of arterial hypertension for at least 30 days prior to
Experimental design

Mean arterial pressure
Heart rate
Portal blood flow
Pulsatility index of hepatic artery

Doppler ultrasound technique

Basal Hemodynamic measurements
Day 1
Basal Hemodynamic measurements
Day 2
Basal Hemodynamic measurements
Day 3

Figure 1: This figure represents the experimental design of the study. In eight liver transplant recipients, hepatic hemodynamic parameters were evaluated under baseline conditions and after placebo, meal ingestion, and isosorbide dinitrate.

2.2. Methods. Hepatic hemodynamic parameters measured using a Toshiba SSA 270 A (Tokyo, Japan) duplex scanner, consisting of a real-time, two-dimensional ultrasonic device and an attached 3.5 MHz pulsed Doppler flowmeter. After a sampling marker had been set in the middle of the lumen of the portal vein along the beam axis, a second marker was positioned parallel to the direction of blood flow. Care was taken to maintain the angle 0 (the angle formed by the ultrasonic beam and the direction of blood flow) below 60, since the accuracy of the measurements decreases at increasing angles. Measurements were carried out during expiration because it can be standardized easily and allows better visualization of the portal vein for Doppler as the angle is reduced to a minimum [4, 5].

Blood flow was obtained by multiplying the blood velocity by the cross-sectional area of the vessel, calculated on the basis of the inner diameter and assuming circular geometry. The pulsatility index of the hepatic artery (calculated as {peak systolic frequency shift − minimum diastolic frequency shift}/peak systolic frequency shift) was determined manually by using calipers, and an average of two to three waveforms were seen in each scan. Doppler evaluation was always carried out by the same specialized examiner (DA).

Arterial pressure was measured with a sphygmomanometer and expressed as mean arterial pressure according to the formula (systolic pressure + diastolic pressure × 2)/3.

2.3. Design of the Study. After an overnight fast, subjects were transferred to the hemodynamic lab, where eco-Doppler measurements were performed. Each liver transplant recipient was randomly assigned to receive placebo (water), a standard mixed liquid meal (355 Kcal, Ensure Plus, Ross Laboratories, Columbus, OH, USA) or isosorbide dinitrate (5 mg, SL) in a cross-design on 3 consecutive days. The experimental design of the study is shown in Figure 1. The randomization was performed by computer. Neither the patients nor the ultrasonographer was aware of the subject’s treatment. Hemodynamic measurements were performed at baseline conditions and 15 and 30 min after both stimuli.

2.4. Statistical Analysis. Results are expressed as mean ± SD. Systemic and hepatic arterial response to portal flow variations were compared using Student’s paired t-test. Differences were considered significant when P was less than 0.05.

3. Results

3.1. Baseline Data. Measurements of systemic and splanchnic hemodynamic parameters in liver transplant recipients are shown in Table 1. Heart rate, mean arterial pressure, and pulsatility index of the hepatic artery (PI) are similar to those observed in healthy subjects. However, an increase in portal blood flow occurs 6 months after liver transplantation. Values of healthy subjects in our lab are 80 ± 5 beats/min for heart rate, 95 ± 5 mmHg for mean arterial pressure, 900 ± 80 mL/min for portal blood flow, and 0.7 ± 0.1 for PI. In patients who administered meal ingestion or isosorbide dinitrate during the first day and placebo the day after, no statistically significant differences were observed between basal values for the 2 days (data not shown). The variability for hemodynamic measurements in consecutive days between basal values was lower than 10%.

3.2. Effects of Portal Blood Flow Variations in Liver Transplant Recipients. Meal ingestion caused a significant increase of portal blood flow in every OLT recipient studied. The maximum effect was observed 30 min after meal ingestion (data not shown); this time was chosen to express hemodynamic changes. The mean PI rose significantly (P < 0.05) from 0.7 ± 0.2 to 0.8 ± 0.2, suggesting a decrease in hepatic artery flow in liver transplant recipients (Table 2). No significant changes were observed in heart rate and mean arterial pressure.

The sublingual administration of 5 mg of isosorbide dinitrate caused a significant reduction of portal blood flow (from 1660 ± 270 to 1397 ± 250 mL/min, P < 0.05) (Table 2). This effect reached its maximum at 15 min, which was the time chosen to express hemodynamic changes. The reduction of
Portal blood flow was accompanied by a significant increase in hepatic arterial flow manifested by a decrease of PI (from 0.7 ± 0.2 to 0.5 ± 0.2, P < 0.05). Mean arterial pressure was significantly reduced after drug administration (from 84 ± 3 to 78 ± 2 mmHg, P < 0.05); heart rate was unchanged (from 76 ± 3 to 77 ± 2 bpm, ns).

Placebo administration had no significant effects on systemic and splanchnic hemodynamic parameters in liver transplant recipients.

### 4. Discussion

Our results show that Doppler technique allows noninvasive measurements of the two components of hepatic blood flow in liver transplant recipients. Moreover, the variations of portal blood flow show that the hepatic arterial buffer response is preserved in the newly implanted liver.

Until now, the hepatic arterial buffer capacity is not easy to quantitate; this is because changes in portal blood flow must be induced in the absence of reflex and hormonal or arterial pressure changes. These conditions are virtually impossible to attain in human. Moreover, separating the hepatic arterial and portal venous components of the liver blood flow is complex. However, with the introduction of noninvasive methods, such as Doppler, measurements of these two components can be performed in patients with cirrhosis and in liver transplant recipients [3, 9–11]. Several reports, from our and other laboratories, have demonstrated the reliability of this technique for evaluating portal hemodynamic changes under physiological and pharmacological stimuli in patients with portal hypertension and in liver transplant recipients [9–11]. Moreover, this technique is also useful to evaluate the resistive index or the pulsatility index of the hepatic artery, an indirect measurement of the hepatic arterial perfusion [12–14].

Many years ago, it was suggested that hepatic metabolic supply and demand regulated hepatic arterial blood flow in the same way as arterial blood flow was regulated in other organs. More recently, it is shown that the primary intrinsic regulation of liver blood flow is mainly due to a reciprocal portal vein-hepatic artery flow relationship [4]. Interestingly, when portal blood flow decreases, hepatic arterial blood flow increases. Conversely, an increase in portal flow leads to a reduction in arterial flow. The compensation of hepatic arterial blood flow for the decreased portal venous blood flow is in the range of 20–30% [4, 15, 16]. This hydrodynamic interaction is defined as the hepatic arterial buffer response [4]. Several authors have investigated the physiology of this response. In this regard, it is postulated that the variations of flow are due to the clearance of an intrahepatic arterial vasoconstrictor (adenosine) to which the hepatic artery is very sensitive [17–19]. Indeed, adenosine has been shown to be a potent vasodilator of the hepatic artery [17–19]. When portal blood flow decreased, the concentration of adenosine is thought to increase, thus resulting in arterial dilatation. The exact location of the synthesis and stockade of adenosine is unknown, but it is postulated to be in the space of Mall, which is the zone surrounding the hepatic arterial resistance vessels and portal venules [17–19].

It is known that the liver is innervated through sympathetic and parasympathetic nerves. Its neural regulation is based on a balance between alpha- and beta-sympathetic nerve activity, which is probably mainly responsible for the adrenergic regulatory effects on liver blood flow [20–22]. Hepatic inflow control is determined by both extrinsic and intrinsic factors, which regulate the hepatic artery vascular resistance and the flow. One of the extrinsic factors, such is the case of cardiac output and splanchnic blood flow, is the hepatic innervation. At present, liver transplantation is an excellent model to study the effect of hepatic denervation on the regulation of liver blood flow. Kjaer et al. have demonstrated that one year after liver transplantation, within the same time when our patients were evaluated, hepatic norepinephrine and epinephrine concentrations are still significantly lower than in nontransplanted livers, suggesting that within the first year after transplantation there is no evidence of sympathetic nerve reinnervation in liver-transplanted patients [23]. Otherwise, clinical studies have evaluated the hepatic arterial buffer response in human transplanted livers [24, 25]. These authors showed that this hemodynamic response is intact in the newly implanted liver [24, 25]. However, it is important to note that most of these previous investigations

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**Table 1: Systemic and splanchnic hemodynamic parameters in healthy subjects and in cirrhotic patients undergoing liver transplantation.**

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>After 6 months of OLT</th>
</tr>
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<tbody>
<tr>
<td>Heart rate (b/min)</td>
<td>80 ± 5</td>
<td>80 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>95 ± 6</td>
<td>98 ± 7</td>
</tr>
<tr>
<td>Portal blood flow (mL/min)</td>
<td>900 ± 80</td>
<td>1660 ± 270*</td>
</tr>
<tr>
<td>Pulsatility index of hepatic artery</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.2</td>
</tr>
</tbody>
</table>

* Mean ± SD, *P < 0.05.

**Table 2: Buffer response study. The effects of standard meal ingestion and isosorbide dinitrate administration on hepatic hemodynamics.**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Meal ingestion</th>
<th>Basal</th>
<th>Isosorbide dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal blood flow (mL/min)</td>
<td>1495 ± 260</td>
<td>2609 ± 250*</td>
<td>1660 ± 270</td>
<td>1397 ± 250*</td>
</tr>
<tr>
<td>Pulsatility index of hepatic artery</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2*</td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.2*</td>
</tr>
</tbody>
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Mean ± SD, *P < 0.05.
have been performed on anesthetized patients during liver transplantation [24, 25]; results of such studies might differ from those performed on conscious subjects. In this regard, experimental data showed that anesthetic drugs may alter the buffer response [26, 27]. Moreover, measurements of hepatic artery and portal blood flows were performed mainly using electromagnetic flowmeters, a technique that requires precise fitting of the probe and more extensive vessel preparation [28, 29]. With this method the results could be conflicting and unsatisfactory [27, 28]. To our knowledge, this is the first study which examines the buffer response in patients who underwent liver transplantation in stable conditions and without any factor you can alter this physiological response.

In conclusion, Doppler technique is a valuable tool for noninvasive evaluation of the hemodynamic changes associated with physiological stimulus in liver transplant patients. Moreover, our results showed the persistence of the HABR in a denervated human model, suggesting that this physiological mechanism is independent of the regulation from the autonomic nervous system.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


