



# $\beta$ -Blockers Improve Presinusoidal Portal Hypertension

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## Abstract

**Background** Presinusoidal portal hypertension is a clinically important cause of gastric and gastroesophageal varices. Whereas  $\beta$ -blockers have an established prophylactic role against bleeding from esophageal and gastric varices in portal hypertension due to cirrhosis, the effect on presinusoidal portal hypertension is unknown.

**Aims** To evaluate the hemodynamic effect of  $\beta$ -blockers in non-cirrhotic patients with presinusoidal portal hypertension.

**Methods** We measured the blood pressure gradient from spleen pulp to free hepatic vein in 12 patients with presinusoidal portal hypertension by combined hepatic vein catheterization and spleen pulp puncture while on and off  $\beta$ -blocker treatment (random sequence).

**Results** The  $\beta$ -blockers reduced the gradient from a mean off-treatment value of 32 mm Hg to a on-treatment value of 26 mm Hg ( $P < 0.05$ ) with a reduction of at least 20% in five patients (42%).

**Conclusions**  $\beta$ -blocker treatment caused a clinically significant reduction in the pressure gradient from spleen pulp to the free hepatic vein. This finding supports the recommendation for prophylactic  $\beta$ -blockage in patients with presinusoidal portal hypertension.

**Keywords** Gastroesophageal varices · Non-cirrhotic portal hypertension · Portal vein thrombosis · Splenic vein thrombosis · Propranolol

## Introduction

Presinusoidal portal hypertension is a rare but clinically important cause of bleeding gastric and gastroesophageal varices that can be difficult to manage. In contrast to the well-established role of nonselective  $\beta$ -blockers as primary and secondary prophylaxis against variceal bleeding in patients with cirrhosis and intrahepatic portal hypertension, there is no study addressing the hemodynamic effect of  $\beta$ -blockage on presinusoidal portal hypertension, viz., the pressure gradient between the spleen pulp and the free hepatic vein. Clinical recommendations and guidelines, such as the Baveno VI Consensus Workshop, pragmatically

recommend patients with prehepatic portal hypertension be treated with  $\beta$ -blockers as secondary prophylaxis while acknowledging the lack of evidence for the recommendation [1, 2].

The hemodynamic basis for the recommendations for patients with cirrhosis is hepatic vein catheterizations with measurements of the effect of  $\beta$ -blockers on the hepatic venous pressure gradient (HVPG) [3–6]. In presinusoidal portal hypertension, the crucial blood pressure gradient is upstream to the liver which can be measured by combined hepatic vein catheterization and direct percutaneous, thin-needle puncture of the spleen [7]. We use this technique as a clinical procedure and have found it to be safe [8] in agreement with a recent meta-analysis that found the complication rate from thin-needle spleen biopsies to be as low as that of liver and kidney biopsies [9].

Using traditional hepatic vein catheterization in combination with direct spleen pulp puncture, we prospectively evaluated the effect of treatment with  $\beta$ -blockers on the spleen to free hepatic vein pressure gradient in patients with

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presinusoidal portal hypertension by measurements off and on  $\beta$ -blocker treatment.

## Materials and Methods

### Patients

This is a prospective on- and off-treatment case series of 12 non-cirrhotic patients (three female and nine male; median age of 49 years, range 22–79) with presinusoidal portal hypertension. All were normoweight based on body mass index (20–27 kg/m<sup>2</sup> body surface) except ID 8 (44 kg/m<sup>2</sup> body surface). Clinical characteristics are given in Table 1, and all diagnoses were based on standard clinical workup. All patients had clinically stable disease. Three patients (IDs 2, 9, and 10) had presinusoidal portal hypertension due to intrahepatic obstruction, while the remaining nine had prehepatic obstruction. Individual causes and etiology are given in Table 1. Type and degree of varices are also shown; four patients had experienced bleeding episodes from the varices, eight patients received anticoagulant therapy, and five patients were treated endoscopically (banding). Based on clinical risk assessment and in accordance with the prevailing guidelines [3], we offered the patients a treatment with  $\beta$ -blockers in an attempt to reduce the risk of index or repeat bleeding episodes. Dosage was 80 mg propranolol/day.

The pressure measurements were performed after an overnight fast with catheterization of the hepatic vein and direct spleen pulp puncture. The procedures were conducted according to our clinical guidelines as described below. Initiation of the treatment did not await the hemodynamic measurement, and if started before the first measurement, it was

paused for 5 days before the procedure. Thus, in ten patients, the first investigation was off  $\beta$ -blocker treatment (four of the patients had already started treatment with  $\beta$ -blocker and therefore paused treatment for the first measurement), and median time between the two measurements was 4 months (range 1.5–18 months). Other medications (such as diuretics) were dose-adjusted as necessary between the investigations, but treatments were neither initiated nor stopped.

None of the patients underwent splenectomy before or during the treatment.

### Ethics

The procedures were conducted clinically to evaluate the hemodynamic effect of  $\beta$ -blocker treatment in the same way as our clinical management of patients with cirrhosis and portal hypertension. In patients who paused  $\beta$ -blocker treatment for the off-treatment measurement, we considered the infinitesimal risk of withholding the treatment for 5 days to be outweighed by the benefit of avoidance of non-efficacious treatment and its potential side effects. We did not experience significant complications to the spleen puncture procedure conducted as described below. The data we present were retrieved from the clinical records of the procedures and from the electronic patient records. As with all the other clinical procedures, the patients were carefully informed about risks and benefits beforehand.

### Hepatic Vein Catheterization

With the patient in supine position, a 6.7-F catheter of the Courmand type (Cook, Denmark) was inserted into a right hepatic vein through an introducer placed

**Table 1** Patients

Subject	Sex/age	Diagnosis	Etiology	Varices	Therapy	$\Delta$ pressure (%)
1	F/41	PVT, SVT	Idiopathic pancreatitis	Grade 1 esophageal (bled)	Banding AC	–40
2	M/22	Intrahepatic portal hypoplasia	Congenital	Grade 2 esophageal + gastric	AC	–13
3	F/54	PVT	Pregnancy	Grade 1 esophageal (bled)	Banding	–1
4	M/63	PVT	Polycythemia vera	Grade 2 esophageal (bled)	Banding	–14
5	M/43	PVT	Glucagonoma	Gastric	AC	–35
6	M/49	PVT, SVT, PaVT	Gallstone-induced pancreatitis	Grade 1 esophageal	AC	7.5
7	M/54	SVT	Gallstone-induced pancreatitis	Gastric	None	–34
8	F/49	PVT, SMVT	Elevated factor VIII	Grade 2 esophageal + gastric	AC	–3
9	M/32	Portal sclerosis	Idiopathic	Grade 2 esophageal + gastric	Banding	–7
10	M/79	Portal sclerosis, PVT	Idiopathic	Grade 3 esophageal + gastric	AC	3
11	M/58	PVT	Elevated factor VIII	Grade 2 esophageal	AC	–23
12	M/22	PVT	Protein C deficiency	Grade 1 esophageal (bled)	Banding AC	–56

F female; M male; PVT portal vein thrombosis; SVT splenic vein thrombosis; SMVT superior mesenteric vein thrombosis; PaVT pancreatic vein thrombosis; AC anticoagulant treatment;  $\Delta$  pressure the change in spleen to free hepatic vein pressure gradient between on and off treatment (%)

percutaneously in the right femoral vein. The tip of the catheter was advanced into the wedged position and the pressure was measured. The tip was then retracted to the free position for pressure measurement. The position of the tip was verified by fluoroscopy and injection of X-ray contrast (5–20 mL Omnipaque 240 mg I/mL; Nycomed DAK, Denmark).

### Spleen Pulp Puncture

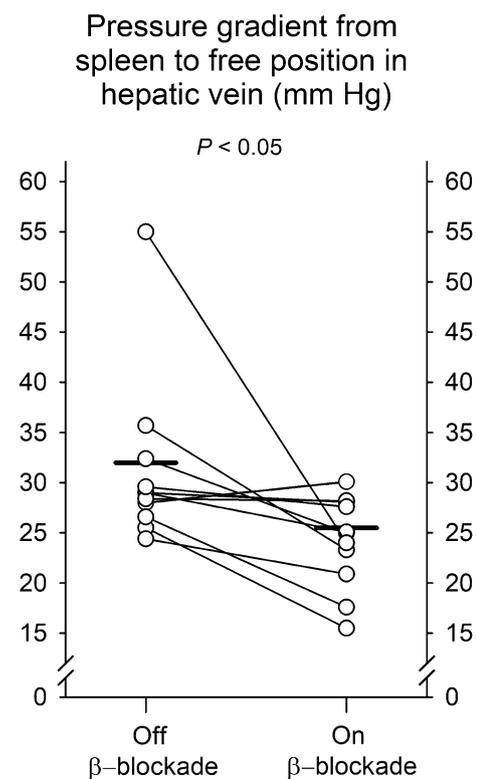
The patient tilted slightly to the right with the left arm over the head. The spleen was visualized by ultrasound, and local infiltration anesthesia of the skin and peritoneum was applied (Lidocain, 10 mg/mL, 5 mL; Danish Hospitals' Pharmacy, Copenhagen). The puncture site was just below the left curvature of the ribs. The patient held his/her breath for up to 20 s, while a 20-G 12-cm-long needle (diameter 0.9 mm, Mediplast, Japan) was introduced into the spleen in a cephalad direction at an angle of 30° to the transverse plane in order to minimize the risk of lacerating the spleen if the patient accidentally took a deep breath during the procedure [6, 7]. The needle was inserted under ultrasonic guidance and advanced into the spleen until the tip was located in the central part of the parenchyma where the pressure was recorded.

### Statistical Analysis

Intra-individual difference between on- and off-medication pressures was tested by a paired *t* test of the mean difference. A *P* value < 0.05 was considered an indication of a statistically significant effect of treatment. On the individual level, we considered a pressure gradient change of > 5% to be detectable. Due to the homogenous nature of this clinical data set, a sensitivity analysis was performed. This considered the potential influence of including patients with portal versus splenic vein thrombosis and the potential effect of treatment on HVPG; none of these factors affected the statistical results, and the patients are therefore presented as one group.

### Results

Individual changes in pressure gradient are shown in Table 1. For the group as a total, the β-blocker treatment was associated with a mean decrease in spleen to free hepatic vein pressure gradient of 14% with a mean gradient off treatment of 32.0 mm Hg (range 24.4–55.0 mm Hg) versus 25.5 mm Hg (range 15.5–40.8 mm Hg) on treatment (*P* < 0.05) (Fig. 1). The gradient decreased in nine patients and was unchanged in three. Five patients (42%) obtained a gradient reduction of at least 20%.



**Fig. 1** Individual pairs of blood pressure gradients from spleen pulp to free position in hepatic vein in patients with presinusoidal portal hypertension. Each subject was investigated off (left) and on (right) treatment. Mean values for the groups are represented by horizontal lines

The mean off-treatment HVPG was 4.0 mm Hg (range 1.0–9.0 mm Hg) and was unaffected by β-blockade (*P* = 0.97).

The mean off-treatment pressure in the spleen pulp was 34.5 mm Hg (range 25.6–50.0 mm Hg) which decreased on treatment to 28.6 mm Hg (range 16.3–34.7 mm Hg) (*P* < 0.05). In six patients (50%), the pressure in spleen pulp decreased by at least 20% on treatment when compared to off treatment (*P* < 0.05).

There were no statistical relationships between treatment effect and propranolol dose/BMI, heart rate, or arterial blood pressure (*P* > 0.30 for all, data not shown).

### Discussion

The main result of this first systematic study of the hemodynamic effects of β-blockers on presinusoidal portal hypertension is that the treatment caused a significant reduction in the pressure gradient from spleen to the free hepatic vein position.

Current treatment options for patients with newly identified thrombosis in the portal or splenic vein are limited to

anticoagulant therapy, trans-vascular thrombectomy, or, in highly selected cases, surgery [1, 10–14]. For patients with intrahepatic presinusoidal portal hypertension, we have no treatment. We believe that our findings provide pathophysiologic rationale to the pragmatic recommendation of treating patients with presinusoidal portal hypertension with  $\beta$ -blocker as primary and secondary prophylaxis against variceal bleeding [2–6]. The findings may also explain the beneficial effect of propranolol on recurrent bleeding episodes in patients with non-cirrhotic portal fibrosis due to schistosomiasis [15].

To what extent the hemodynamic effect of the  $\beta$ -blockage translates into the desired clinical effects, i.e., a decrease in the number of bleeding episodes, requires larger long-term observational studies, and for a definitive recommendation, randomized controlled trials are needed. Such trials will be difficult to conduct because of the rarity of the condition, and because not all patients with presinusoidal portal hypertension develop bleeding varices, a high number of patients will be needed. However, we do believe that our results motivate such a multicenter trial.

Atkinson and Sherlock found the spleen pulp pressure in normal man to be 10 mm Hg with an upper normal value of 17 mm Hg [7]. Off treatment, all our patients were above this upper threshold, confirming prehepatic portal hypertension. The risk of bleeding is determined by the intra-variceal pressure [10], which in case of presinusoidal portal pressure is determined by the reported pressure gradient. A pressure gradient reduction of at least 20% is desirable, if analogous to the situation in cirrhosis, and this was observed in 5/12 patients, viz., 42%.

Propranolol is shown to decrease the portal pressure by lowering the splanchnic inflow in portal vein-constricted rats, but a concomitant increase in portocollateral resistance counteracted the decrease in portal pressure [16]. This was not the case in rats with CCl<sub>4</sub>-induced cirrhosis and mild portosystemic shunting [17]. The extent of portosystemic shunting in patients with presinusoidal portal hypertension might thus diminish the response to propranolol. However, we did not find any clinical evidence of a more pronounced portosystemic shunting in the nonresponders in our patients. Furthermore, we found the same response rate (42%) as we did for the postsinusoidal portal hypertension in patients with cirrhosis [4].

In conclusion, we observed a clinically meaningful reduction in the blood pressure gradient from spleen pulp to the free hepatic vein by  $\beta$ -blocker treatment in patients with presinusoidal portal hypertension. Our data thus support the guideline recommendations of offering this treatment to such patients, but documentation of its clinical outcome benefit awaits studies with clinical end points.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of Interest.

**Ethical Statement** For this type of study, formal consent is not required.

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