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Effect of ET-A blockade on portal pressure and hepatic arterial perfusion in patients with cirrhosis: A proof of concept study

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Abstract

Background/aim: Endothelin causes vasoconstriction via the endothelin-A receptor (ET-A) in the intrahepatic circulation in cirrhosis and its increase leads to portal hypertension. The aim of the study was to investigate the acute effect of a selective ET-A antagonist in patients with portal hypertension and cirrhosis.

Methods: Proof-of-concept study with two different substudies: (a) local intrahepatic administration of the ET-A antagonist BQ 123 and (b) systemic oral administration of the ET-A antagonist Ambrisentan. Portal pressure was determined by hepatic venous pressure gradient (HVPG, both substudies) and hepatic arterial blood flow (HABF) by intra-arterial Doppler measurements (substudy 1) before and under the ET-A antagonist. Systemic haemodynamic parameters were measured in substudy 2.

Results: Twelve patients (Child-Pugh [CP] B/C n = 7/5) were included in substudy 1 and 14 patients (CP A/B/C n = 4/6/4) in substudy 2. The relative decrease in HVPG was −12.5% (IQR: −40% to 0%; $P = .05$) in substudy 1 and −5.0% (IQR: −11.5% to 0%; $P = .01$) in substudy 2. Substudy 1 revealed higher decrease in HVPG in CP B patients. HABF increased significantly and patients without portal pressure decrease showed a higher increase of HABF. Substudy 2 showed a slight decrease in the mean arterial pressure without changes of other systemic haemodynamic parameters.

Conclusion: Administration of a selective ET-A antagonist decreases the portal pressure in cirrhotic patients. This decrease was higher in CP B patients and the non-responders showed a higher increase in hepatic arterial flow. Selective ET-A antagonists might be a future treatment option in patients with portal hypertension.

KEYWORDS

cirrhosis, endothelin, haemodynamics, hepatic venous pressure gradient

Clinical trial number: KKHS-042-Endothelin.

1 | INTRODUCTION

Portal hypertension is caused by both an increase in intrahepatic vascular resistance and an increase in portal venous flow because of splanchnic vasodilation.[1] Although structural changes play a major role, a smaller proportion of the increased intrahepatic vascular resistance is because of vasoconstrictor/vasodilator imbalance in the sinusoidal/presinusoidal area, in favour of the former. Different drugs have demonstrated a reduction in portal pressure in patients with cirrhosis by acting on this balance, mainly by increasing the availability of NO.[2,3]

The liver is, however, unique in its vascularisation with not only portal venous but also arterial blood supply, which converges in the presinusoidal and sinusoidal area.[4] In vivo, in a normal healthy state, these two circulatory systems are regulated in order to maintain a circulatory homoeostasis, so that with decreased portal flow (and therefore reduced portal venous blood supply) an arterial vasodilation occurs.[5] This phenomenon is known as the hepatic arterial buffer response.[6] Two independent mechanisms regulate the hepatic arterial blood flow: one which is dependent on portal venous flow (ie hepatic arterial buffer response), and the other which is independent of portal venous flow.[7-9]

Endothelin, produced by the endothelium, is one of the most potent vasoconstrictors which has been identified, although its effect depends on the receptor with which it interacts.[10] Two main G protein coupled receptors have been identified, namely ET-A and ET-B.[11] While interaction with ET-A causes vasoconstriction, interaction of ET-B in endothelial cells leads to vasoconstriction but also induces the release of vasodilators such as nitric oxide, so that its net effect is vasodilatory. In the healthy liver, there is a higher concentration of ET A than ET B receptors, so that in normal conditions the net effect of endothelin-1 in this vascular territory is vasoconstriction.[12] In portal hypertenstion, an increase in intrahepatic endothelin-1 signalling has been described.[13] Indeed several studies in animal models of cirrhosis have shown that blockade of endothelin with the non-selective endothelin blocker Bosentan leads to a reduction in portal pressure.[14,15] Studies evaluating the hepatic haemodynamic effect of endothelin blockade in patients have used non-selective drugs, so that the net effect on portal pressure may have been underestimated.[16,17] Indeed, the recent study using non-selective Endotheilin-blocker Macitentan could not detect a significant reduction of HVPG.[17] The haemodynamic effects of selective ET-A blockade in cirrhosis has been previously evaluated in only one study, in which no effect was observed perhaps masked by the small sample size (n = 8 per group).[18]

The aim of the present study was to evaluate the effect of a selective ET-A blockade on portal pressure as estimated by the hepatic venous pressure gradient in patients with cirrhosis. The secondary aim was to evaluate the effect of this drug on hepatic arterial blood flow. In order to carry this out, two substudies were performed, which differ mainly according to the administration of the selective ET-A blocker: intra-arterial (local) and oral (systemic).

2 | METHODS

This study is a prospective proof of concept acute haemodynamic study. Patients (between 18 and 75 years of age) with cirrhosis who underwent TIPS evaluation without any exclusion criteria were proposed to participate in the study. Only patients who gave their informed consent were included. Exclusion criteria were patients who had an ongoing infection, patients who had hepatic encephalopathy West Haven Grade II-IV, patients with alcoholic hepatitis or other causes of acute on chronic liver disease, patients with portal vein thrombosis, patients with advanced cancer, patients with transaminases three times above the upper limit of normal and administration of beta-blockers in the previous 72 hours before the haemodynamic study.

Two different substudies were performed: the first substudy was performed to evaluate the local effects of endothelin-A receptor blockade (BQ-123) administered to the hepatic artery. This via of administration was chosen in order to try to minimize the systemic effects of the drug. The second substudy evaluated the systemic oral administration of Ambrisentan, a selective ET-A inhibitor (see Figure 1).

In the first substudy (local administration; n = 12), and on top of the catheterization of the hepatic vein in order to measure the hepatic venous pressure gradient (see below), a catheter was placed into the hepatic artery (see below). This allowed continuous local infusion of a selective ET-A antagonist (BQ-123)[19] at increasing doses, that is, 10 minutes 300, 10 minutes 500, 3 minutes 1000 and 3 minutes 2000 nmol min^{-1}, and simultaneous and continuous measurement of the hepatic arterial blood flow with a Doppler wire.[9,20] The increasing doses were chosen because of safety reasons. This selective ET-A inhibitor has a high first pass hepatic metabolism,[21] so that it is expected that almost no drug reaches the systemic circulation and therefore the effects observed in the hepatic artery would be because of its local effect. A specific exclusion criteria for this study was the presence of a stenosis of the celiac trunk because of arteriosclerotic plaques with regard to the increased technical difficulties this could lead to.

In the second substudy (systemic administration; n = 14), patients underwent catheterization of the hepatic vein and measurement of the hepatic venous pressure gradient as well as right heart catheter and percutaneous ultrasound Doppler of the hepatic artery with measurement of the resistance and pulsatility index before and 90 minutes after the oral administration of Ambrisentan (oral ET-A blocker, dose 5 or 10 mg, Volibris GlaxoSmithKline). The dose of Ambrisentan was chosen according to the recommended dose for treatment of pulmonary hypertension. Owing to safety aspects, regulatory authorities (Bundesministerium für Arzeneimittel und Medizinprodukte, BfArM) required an initial lower dose of 5 mg in the first 10 patients. The results were then reported back before the rest of the patients could be administered the higher 10 mg dose. Non-invasive blood pressure measurement, heart rate and peripheral oxygen saturation were measured throughout the whole study.

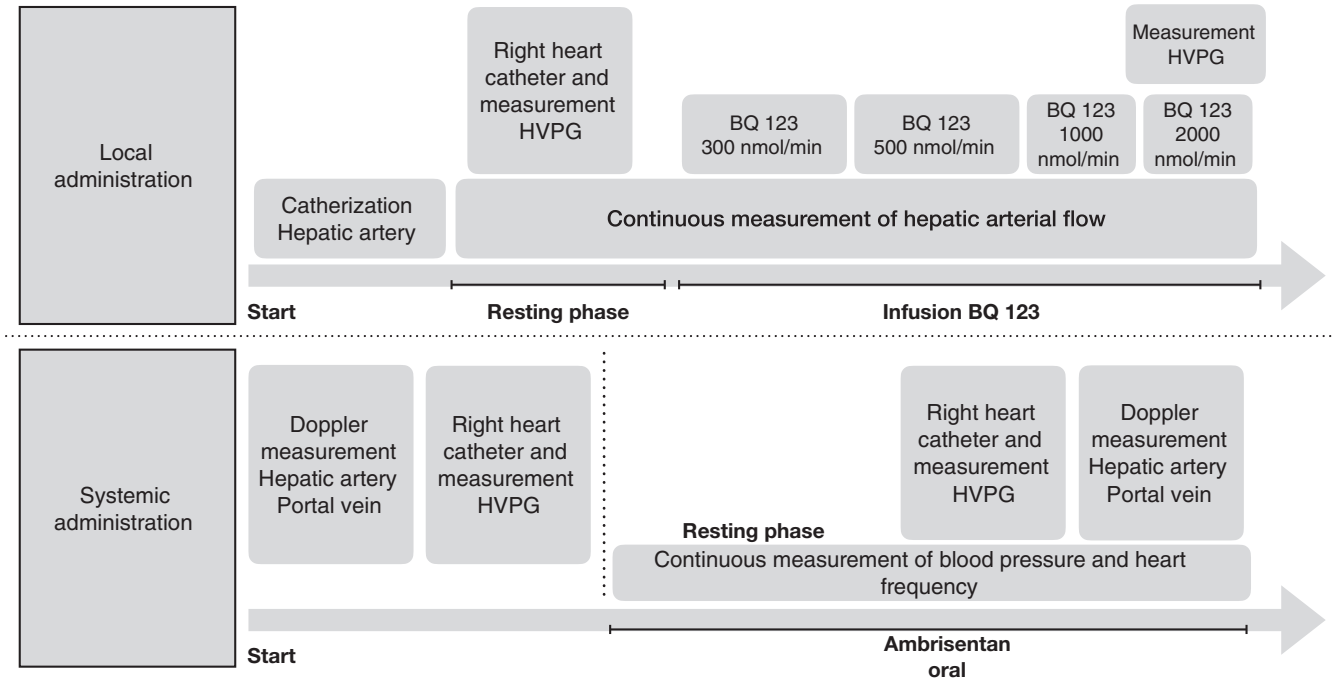

FIGURE 1 Schematic diagram of the two different experimental settings. Note that the length of the boxes and time frames are arbitrary

2.1 | Hepatic vein catheterisation

The haemodynamic study was performed after an overnight fast. After local anaesthesia, a 9F vascular introducer sheath (Boston Scientific) was placed into the right internal jugular vein according to Seldinger's technique. Afterwards, a 7F balloon catheter (Cordis SA) was inserted into the right hepatic vein, approximately 2-3 cm from the vena cava, in order to assess free and wedged hepatic venous pressure (FHVP and WHVP). The zero-pressure level was set in the mid-axillary line. The hepatic venous pressure gradient (HVPG) was calculated as WHVP minus FHVP. Each measurement was performed in triplicate after at least 1 minute of stabilization. Two different investigators evaluated the tracings, one of whom was blinded to the chronological order and therefore to the presence or absence of endothelin.

2.2 | Right heart catheterization

In the substudy 2 (systemic administration), besides the hepatic haemodynamic study, a Swan-Ganz catheter (Edwards Lifesciences) was inserted into the right pulmonary artery to determine mean pulmonary arterial pressure (MPAP; mm Hg), pulmonary capillary wedge pressure (PCWP; mm Hg) and right arterial pressure (RAP; mm Hg). The cardiac output (CO; L min^{-1}) was measured by the thermodilution technique, with the average of at least three consecutive values, allowing a maximum difference of 0.5 L min^{-1} between them. The haemodynamic parameters were permanently recorded. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated with the following formulae, respectively: SVR = (MAP-RAP) × 80/CO; PVR = (MPAP-PCWP) × 80/CO, in dyn s cm^{-5}.

2.3 | Hepatic arterial catheterization

In the patients included in substudy 1 (local administration), hepatic arterial catheterization was performed. The technique for hepatic arterial catheterization was done as previously described.[9,20] By using a transfemoral approach, a 5 French guiding catheter was introduced selectively into the hepatic artery. A Doppler wire (Flowire, Cardiometric, diameter 0.46 mm, pulse repetition frequency 40 kHz, pulse duration 0.83 ms, sampling delay 6.5 ms) was used together with a Doppler Instrument (Flomap; Cardiometrics) to measure hepatic arterial peak flow velocities. The average of peak flow velocity (APV) and the pulsatility index (PI; ie the difference between the systolic and diastolic peak flow velocities divided by the APV) over two complete cardiac cycles was calculated. The diameter of the vessel was obtained during the procedure by means of high-resolution angiography at a point 5 mm downstream from the tip of the Doppler wire, in two different perpendicular planes (d1 and d2) before and after the last dose of drug infusion. The cross-sectional area and the hepatic artery blood flow rate (HABF) were calculated according to the following formula (cross-sectional area = 3.14 × d1 × d2 × 0.25; HABF = 0.6 × APV × cross-sectional area).

2.4 | Ultrasound measurements of the hepatic artery and the portal vein

For the patients included in substudy 2 (systemic administration), percutaneous evaluation of the hepatic artery and the portal vein using Doppler measurements was performed. Once the patients had been lying supine for 15 minutes, Doppler measurements were obtained (Aplio XG). A 3.5-5 MHZ convex probe was used. The left

hepatic artery and the portal vein were imaged in B-mode. A maximum insonation angle of 60° was permitted with correction for the insonation angle applied as needed.[22] For the hepatic artery peak systolic velocity, mean velocity and end-diastolic velocity, pulsatility and resistance index and for the portal vein flow velocity were recorded. Measurements were taken in triplicate.

2.5 | Statistical analysis

Data are presented as median and interquartile range (IQR). Categorical data are presented as proportions, while continuous variables are presented with medians and interquartile range. Non-parametrical statistical tests were used. Parameters were evaluated before and after the administration of the drug, so Wilcoxon's matched pairs signed rank test for repeat measurements were used. The Mann-Whitney-Wilcoxon test or ANOVA test was used for comparison between groups. The association between continuous variables was assessed using the Spearman rank correlation. For the analysis of the global effect of endothelin-A blockade on HVPG and hepatic arterial parameters, measurements before and with the highest dose were used. Approval for the study by the Ethics Committee of the University of Halle-Wittenberg was obtained for both studies (KKSH-042-Endothelin). Approval from the appropriate german governmental authorities (Bundesministerium für Arzeneimittel und Medizinprodukte, BfArM Bonn, Germany; Eudra-CT-Number: 2007-005679-33) for the off-label use of Ambrisentan was obtained.

3 | RESULTS

A total of 26 patients were included, 12 patients in the substudy 1 (local administration) and 14 patients in the substudy 2 (systemic administration). The baseline characteristics of the patients are shown on Table 1. Overall, the administration of the endothelin-blockers was well tolerated, no adverse events in the context of the acute administration were detected.

3.1 | Substudy 1 (local administration)

In this study, different doses of a selective ET A Blocker (BQ 123) were infused into the hepatic artery. HVPG decreased from 17 mm Hg [IQR: 11-20] to 14 mm Hg [IQR: 9-19; $P = .05$] as a result of the administration of BQ 123 (Table 2; Figure 2A). This corresponds to a relative decrease of −12.5% (IQR: −40 to 0). The haemodynamic effects were greater and clinically relevant in Child-Pugh B −30% (IQR: −43.8 to −11.8) but not in Child-Pugh C patients −6.2% (IQR: −17.4 to 4.2; Figure 3B). No differences in the baseline HVPG was seen among those who had a clinically relevant reduction of HVPG.

During the administration of BQ123, average peak flow velocity (APV) of the hepatic artery significantly increased ($P = .01$, Table 2), pulsatility index (PI) decreased ($P = .05$, Table 2) and hepatic arterial blood flow (HABF) significantly increased ($P = .01$; Table 2). No differences in the maximal absolute changes of HABF (Figure 3A),

TABLE 1 Baseline characteristics of all patients and according to local and systemic administration. Data presented as median and interquartile range in bracket

	Local administration	Systemic administration
n= (male)	12 (10)	14 (10)
Aetiology alc/viral/NASH/ others (n=)	11/0/0/1	8/0/3/3
Age (y)	45.5 (41.3-61.3)	58.0 (51.0-68.3)
Child-Pugh class A/B/C (n=)	0/7/5	4/6/4
Child-Pugh points	9.0 (9.0-10.8)	8.0 (6.0-10.0)
MELD (points)	13.0 (10.5-16.3)	10.5 (8.8-13.3)
Albumin (g L^{-1})	25.5 (21.0-28.0)	29.5 (21.5-36.0)
Bilirubin (μmol L^{-1})	32.5 (27.5-51.8)	21.0 (18.0-30.5)
Prothrombin time (%)	68.0 (58.0-85.0)	67.5 (60.3-86.3)
Ascites (no/mild/severe)	1/4/7	3/3/8
Cardiac output (L min^{-1})	6.6 (5.5-8.2)	5.1 (4.2-7.0)
Cardiac index (L min^{-1} m^{-2})	3.4 (3.0-3.8)	2.9 (2.3-3.3)
Systemic vascular resistance (dyn s cm^{-5})	875 (822-1297)	1309 (938-1551)
Mean blood pressure (mm Hg)	87.0 (83.0-104.0)	88.0 (80.3-98.0)
Heart rate (bpm)	77.0 (57.0-85.0)	84.5 (76.3-90.0)
Hepatic venous pressure gradient (mm Hg)	17.0 (11.0-20.0)	23.0 (18.8-25.0)

TABLE 2 Median changes (IQR) of systemic and hepatic haemodynamic by intrahepatic (local) administration of the selective endothelin-A blocker

Parameter	Before ET-A blocker	During ET-A blocker	*P* value[a]
Systolic blood pressure (mm Hg); n = 6	114.5 (109.5-124.5)	113.0 (106.8-127.8)	.78
Diastolic blood pressure (mm Hg); n = 6	69.5 (59.5-80.3)	67.5 (60.0-83.3)	1.0
Heart rate (bpm); n = 6	77.0 (68.5-91.3)	84.0 (63.3-98.3)	.65
Hepatic venous pressure gradient (mm Hg)	17.0 (11.0-20.0)	14.0 (9.0-19.0)	.05
Average peak flow velocity (cm s^{-1})	24.0 (16.8-48.1)	30.3 (19.3-57.2)	.01
Pulsatility index	1.5 (1.1-2.6)	1.4 (1.2-1.9)	.05
Hepatic arterial blood flow (mL min^{-1})	206 (135-536)	359 (278-964)	.01

[a]Wilcoxon matched pair signed test.

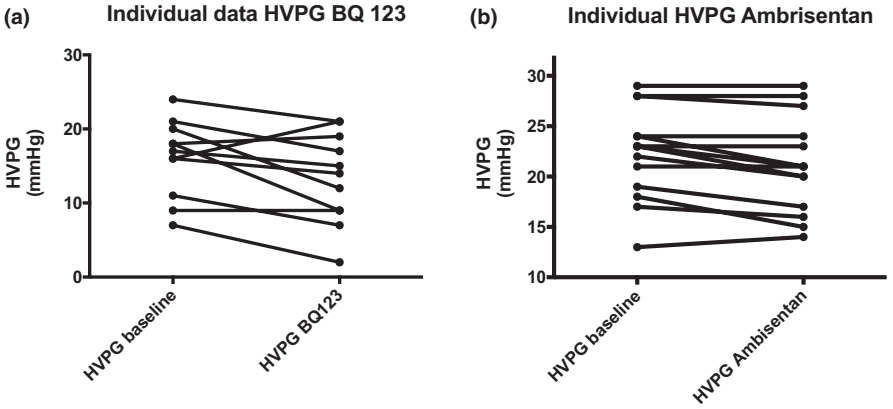

FIGURE 2 Individual data of hepatic venous pressure gradient (HVPG) at baseline and with the presence of BQ123 (A) and Ambrisentan (B)

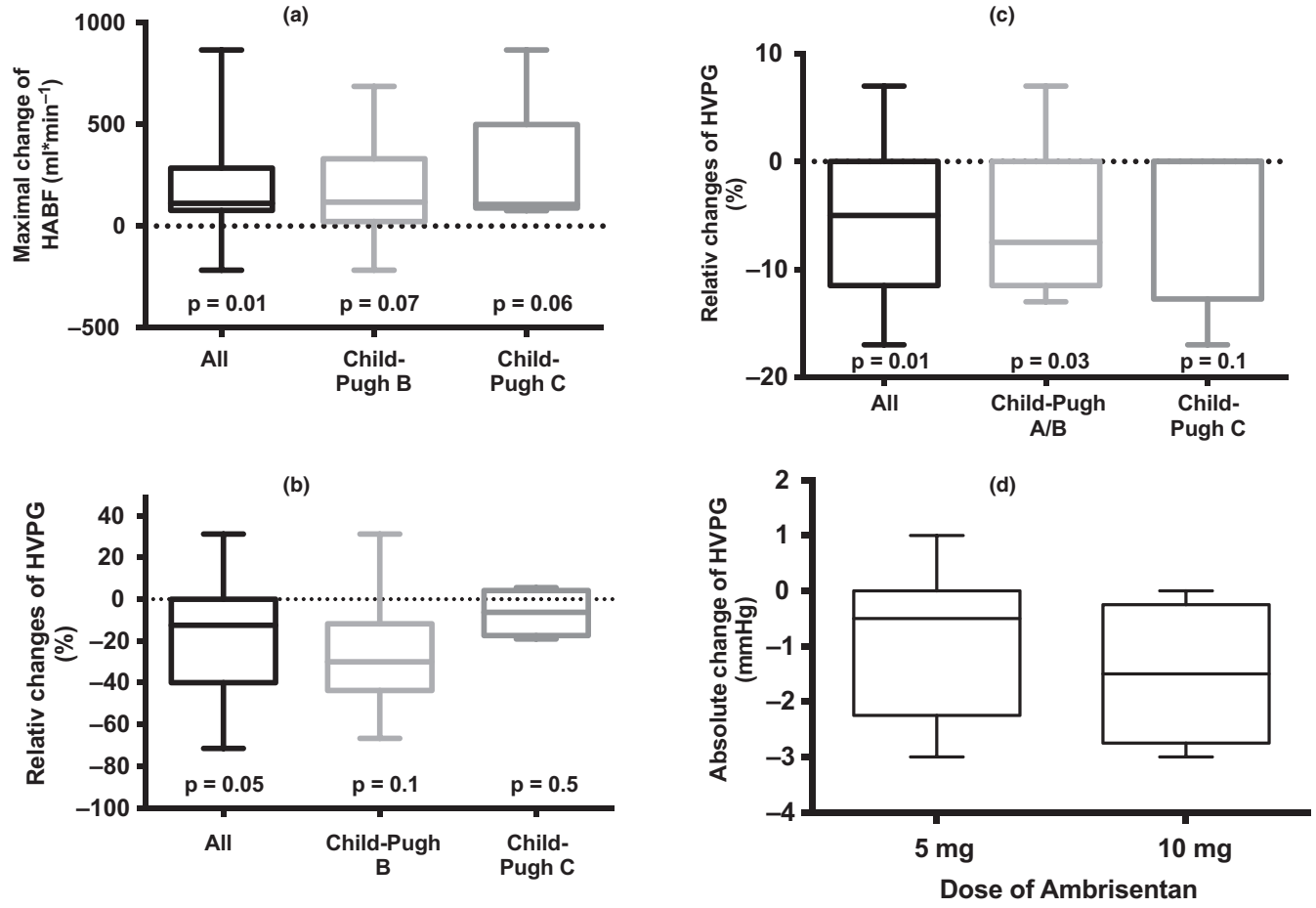

FIGURE 3 Maximal absolute changes in hepatic arterial blood flow (HABF; A) and the relative change of the hepatic venous pressure gradient (HVPG; B) as a result of a local administration of a selective endothelin-A-receptor blocker. Relative changes of the hepatic venous pressure gradient (HVPG) in different Child-Pugh classes (C) and with two different doses (5 and 10 mg; D) owing to an oral systemic administration of the selective endothelin-A-receptor blocker Ambrisentan

of APV (CP-B: 4.1 cm s^{-1} [IQR: 1.0-9.8]; CP-C: 6.9 cm s^{-1} [IQR: −1.8 to 13.3]) and of PI (CP-B: −0.06 [IQR: −0.3 to 0.1]; CP-C: −0.3 [IQR: −1.4 to −0.1]) were observed according to the severity of liver disease. Interestingly, the patients without HVPG response to BQ123 (n = 3) had a higher increase in hepatic arterial flow (responder 92.7 ml min^{-1} [IQR: 35.4-139.4]; non-responder 331.0 mL min^{-1} [IQR: 106.7-866.0]).

3.2 | Substudy 2 (systemic administration)

The effects of the oral administration of the selective endothelin-A blocker on hepatic haemodynamics (hepatic vein catheterization), pulmonary and systemic haemodynamics as measured by right heart catheterization and on the hepatic arterial haemodynamics, as measured by percutaneous ultrasound are shown on Table 3. While

there was a slight but significant decrease in mean arterial pressure (−2.0 mm Hg [IQR: −7.3 to 0.0]; $P = .002$), there were no changes in CO, CI, and SVR. Central venous pressure did not change because of the administration of Ambrisentan ($P = .13$). The decrease in mean pulmonary arterial pressure (mPAP) under Ambrisentan was borderline significant ($P = .054$), whereas the wedge pulmonary pressure had no significant change ($P = .24$; Table 3). There were no changes in the pulsatility ($P = .38$) and resistance index ($P = .93$) of the hepatic artery during the administration of Ambrisentan (Table 3).

The selective endothelin-A blocker led to a significant reduction of HVPG in all patients (−5.0% [IQR: −11.5% to 0.0%], $P = .01$; Figure 2B). There were no differences between the two different doses (Figure 3D). Five patients showed a clinically relevant reduction (ie reduction of 10%) of HVPG. Two patients had a decrease of HVPG but less than 10%. Five patients had no change of HVPG and one patient had an increase (Figure 2B). The relative changes of HVPG are shown in Figure 3C with a significant reduction in Child-Pugh A and B. There were no differences in the magnitude of the reduction of HVPG between patients with Child-Pugh A and B cirrhosis compared to Child-Pugh class C patients ($P = .61$) most likely towing to the small number of patients. There was no correlation between the relative changes of HVPG and Doppler-derived relative changes of portal vein flow ($r = 0.37$; $P = .29$). Additionally, there was no correlation between relative changes of HVPG and relative changes of mean blood pressure ($r = 0.18$; $P = .5$) and relative changes of pulsatility index of the hepatic artery ($r = −0.22$; $P = .43$). Furthermore, there was no correlation between relative changes of the systemic blood pressure and relative changes of the changes in hepatic arterial PI ($r = −0.04$; $P = .88$). In summary, no correlation between relative changes of systemic blood pressure or hepatic arterial Doppler flow parameters and changes in portal pressure could be observed, suggesting that the effect of oral administration of endothelin-A blocker on portal pressure was due its local effect independent from changes in systemic haemodynamics.

TABLE 3 Median changes (IQR) of systemic, pulmonary and hepatic haemodynamics by oral (systemic) administration of the selective endothelin-A blocker

Parameter	Before ET-A blocker	During ET-A blocker	*P* value[a]
Mean blood pressure (mm Hg)	88.0 (80.3-98.0)	85.0 (75.8-95.0)	<.01
Heart rate (bpm)	84.5 (76.3-90.0)	87.5 (72.0-93.5)	.51
Mean hepatic arterial blood flow velocity (cm sec^{-1})	17.0 (12.0-20.0)	17.0 (14.5-21.0)	.22
Portal blood flow velocity (cm sec^{-1})	11.5 (8.0-16.5)	11.5 (8.5-15.3)	.78
Hepatic venous pressure gradient (mm Hg)	23.0 (18.8-25.0)	21.0 (16.8-24.8)	.01
Mean pulmonary arterial pressure (mm Hg)	14.0 (13.0-18.0)	13.0 (11.0-17.0)	.05
Pulmonary wedge pressure (mm Hg)	9.0 (6.3-10.3)	7.0 (5.0-10.0)	.24
Central venous pressure (mm Hg)	5.0 (4.0-5.8)	4.5 (3.8-6.0)	.12
Systemic vascular resistance (dyn s cm^{-5})	1309 (939-1551)	1275 (898-1519)	0.77
Cardiac index (L min^{-1} m^{-2})	2.9 (2.3-3.3)	2.8 (2.4-3.1)	0.15

[a]Wilcoxon matched pair signed test.

4 | DISCUSSION

This study shows a decrease of the portal pressure as estimated by the hepatic venous pressure gradient with the administration of a selective endothelin-A blocker. The findings are seen both with a local and systemic administration of the drug. The changes in HVPG were independent of the changes in systemic haemodynamics. Furthermore, an increase in the hepatic arterial flow was observed and this effect was also independent of the changes in systemic circulation, suggesting that the effect on HVPG is because of a local effect of the endothelin-A receptor blocker.

This result contrasts with the previous study evaluating endothelin blockade in portal hypertension, in which no effect on HVPG was observed.[16-18] The main difference between the studies is that the previous studies used a systemic administration of BQ123,[18] so that the exact dose reaching the liver was unclear or an oral non-selective endothelin blocker which blocked both ET-A and ET-B receptors such as Tezosentan or Macitentan.[16,17] In the present study, a selective ET-A blocker was administered locally and systemically.

Endothelin-1 is one of the key molecules for vasoconstriction in the intrahepatic vascular bed. Several animal and human studies have shown an increased concentration of endothelin-1 in cirrhosis in hepatic tissue and serum.[23-27] Endothelin-1 binds to both receptors, the endothelin-A and endothelin-B receptor,[12] the former with vasoconstrictive properties while the latter has mainly vasodilatory properties. These receptors are found on hepatic stellate cells (endothelin-A receptor) and sinusoidal endothelial cells (Endothelin-B receptor).[28] The hepatic stellate cells are the main cell type responsible for intrahepatic vasoconstriction and are located in the Space of Disse.[28] Once endothelin-1 binds to the ET-A receptor on the hepatic stellate cell, this leads to an increase of inositol triphosphate, diacylglycerol and protein kinase C which in turn leads to vasoconstriction.[28,29] On the other hand, the endothelin-B receptor is located on the sinusoidal endothelial cells and mediates vasodilatation.[28] Therefore, it is logical that inhibition of both receptors leads to a mitigation or lack of effect on HVPG, while use of a selective endothelin-A receptor blocker has a greater effect on HVPG. Indeed, our results indicate a major role of the endothelin-A receptor in the increased intrahepatic resistance in cirrhosis.

Two different routes of administration were used. Firstly, infusion of the endothelin-A inhibitor was done through the hepatic artery. This was undertaken to evaluate the intrahepatic effects of ET-A inhibition, without the interaction of possible effects on systemic haemodynamics. This selective ET-A inhibitor has a high first pass hepatic metabolism in rats, so that after a venous infusion a high total body clearance, comparable to the hepatic blood flow rate, is observed.[21] Indeed, we observed an effect of ET-A blocker on portal pressure with this local route of administration. Interestingly, the effect of the ET-A blocker was of greater magnitude in Child-Pugh B compared to Child-Pugh C patients perhaps because of a higher increase of the hepatic arterial flow in the latter patients (Figure 3A). This contrasts to the previous published study [18] in which no effect on portal pressure was observed. This could be owing to the systemic infusion of this medication with a high first pass mechanism, so that the effective doses reaching the liver are unclear and also due to differences in the study population as only compensated patients were included.

Secondly, a substudy which evaluated the acute haemodynamic effect of oral administration of Ambrisentan, a selective ET-A blocker was undertaken. As expected,[30] the oral administration of Ambrisentan caused systemic and pulmonary haemodynamic effects with a small decrease of mean arterial pressure which was statistically significant but not clinically relevant. However, other relevant systemic haemodynamic parameters like cardiac index or systemic vascular resistance did not change. Furthermore, a reduction in HVPG was observed, which was higher in Child-Pugh A and B patients but did not reach a 10% decrease. This threshold has been shown to be associated to clinical outcomes in compensated patients in the context of treatment with beta-blockers.[31] Whether the clinical benefits of this threshold hold for other drugs who lead to this reduction remains a matter for further investigation.[32] In summary, we can confirm that selective ET-A inhibition leads to a decrease in portal pressure. Furthermore, this effect was dose independent and was not associated to side-effects.

Additionally, the findings of this study further underline the fact that the regulation of the hepatic arterial blood flow is mainly depending on the local conditions with a lesser influence of systemic haemodynamics. Indeed, we observed an increase of the hepatic arterial blood flow using local administration, which was not as marked with the systemic administration. Interestingly, the patients from the former group without response in portal pressure had a higher increase in hepatic arterial flow. This finding confirms previous results in animals[4] in which a greater influence of the hepatic arterial blood flow on portal pressure in cirrhosis was seen. Furthermore, the present study showed that the pharmacological-induced changes in hepatic arterial flow parameters were independent of systemic haemodynamics in humans. This local regulation of the hepatic arterial flow, which overrides changes in the systemic circulation, is most likely because of different systemic and local mediators.[6,33-35] In the systemic circulation of cirrhotic patients the main vasodilatory mediator is nitric oxide[1] while in the hepatic arterial vascular bed there are two main vasodilatory mediators, nitric oxide and adenosine.[6,33,34]

Our study also has some limitations, because of the complicated experimental procedures and the two different routes of administration the number of patients is limited. However, this is a proof-of-concept study investigating the effect of a selective intrahepatic and oral endothelin-A receptor blocker on portal pressure. Future studies are required to evaluate the haemodynamic effects of the oral selective endothelin-A blocker Ambrisentan in the short and long term. Another limitation of our study is the dose of the endothelin-A blocker. No studies have evaluated the appropriate dosage of intrahepatic BQ 123 or oral Ambrisentan to reduce portal pressure in patients with cirrhosis. Therefore we used the dose that was used in other studies[18,19] or was approved by authorities for other indications. If a lower dose had also portal pressure decreasing effects, one could expect that it could be associated with less side effects in the long run. The measurement of hepatic arterial blood flow was performed by two different methods (intra-arterial Doppler wire and abdominal ultrasound) which provide two different parameters namely flow rate and flow velocity, which are related but cannot be compared directly. Finally, our study was conducted in patients with decompensated alcoholic cirrhosis and therefore the results may only be applicable to this aetiology of liver disease.

In conclusion, local and systemic administration of a selective endothelin-A blocker leads to a decrease in portal pressure, which was dose independent. Finally, this is the first study to confirm with direct invasive measurements of previous data from animal studies and indirect data from human studies, that the hepatic arterial flow has an important influence on portal pressure in cirrhosis.

CONFLICT OF INTEREST

None.

FUNDING INFORMATION

None.

AUTHOR CONTRIBUTIONS

AZ, MD, FG planned the study. AZ, MW collected the data. AZ, CR did the analyses and wrote the paper. All authors have provided important intellectual input and have approved the final draft of the paper.

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