The role of hepatic arterial flow on portal venous and hepatic venous wedged pressure in the isolated perfused CCl₄-cirrhotic liver.

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Running title: Role of hepatic artery on wedged pressure

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Abstract

In cirrhosis, hepatic venous pressure gradient is used to measure portal venous and sinusoidal pressures as well as drug induced decreases of elevated pressures. The aim of this study was to investigate the influence of hepatic arterial flow changes on portal venous perfusion (PVPP) and wedged hepatic venous pressure (WP). Normal and CCl₄-cirrhotic rats were subjected to a bivascular liver perfusion with continuous measurements of PVPP, WP, and hepatic arterial perfusion pressure. Flow-pressure curves were performed using different flows either through the portal vein (PVF: 32-20 ml/min) or hepatic artery (HAF: 5-15 ml/min). Increases in HAF lead to significant absolute and relative increases in PVPP (p=0.002) and WP (p<0.001). Absolute changes in HAF correlated to absolute changes in PVPP (cirrhosis: r=0.64, p<0.001; control: r=0.67, p<0.001) and WP (cirrhosis: r=0.71, p<0.001; control: r=0.82, p<0.001). Changes in PVPP correlated to changes in WP due to changes in PVF only in cirrhosis (r=0.75, p<0.001) while changes in HAF correlated in both cirrhosis (r=0.92, p<0.001) and control (r=0.77, p<0.001). In conclusion, increases and decreases in HAF lead to respective changes in PVPP and WP. This suggests a direct influence of HAF on PVPP and WP most likely due to changes in sinusoidal perfusion.

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Introduction

The liver has a dual blood supply through the portal vein and the hepatic artery. Portal venous blood flow corresponds to approximately 70-80 % and hepatic arterial blood flow to approximately 20-30 % of the total liver blood flow in humans. In cirrhosis, intrahepatic vascular resistance is increased due to structural and functional changes (31). Furthermore, vasodilation in splanchnic and systemic circulation leads to an increase of portal venous inflow, the total amount of blood entering the portal system (31). Large part of this flow escapes through portal-systemic collaterals. However, both, increased intrahepatic vascular resistance and increased portal venous inflow, cause an increase in portal venous pressure (PVP), which has been defined as the interaction between portal venous flow and the resistance the liver is offering to this flow (12). On the other hand, these intrahepatic and systemic hemodynamic changes in patients with cirrhosis lead to changes of hepatic arterial flow that is also influenced by local factors (15, 18).

The wedge hepatic venous pressure (WHVP), a reflection of sinusoidal pressure, as well as hepatic venous pressure gradient (HVPG), i.e. the difference between WHVP and free hepatic venous pressure, are used to estimate elevated sinusoidal and portal venous pressures in cirrhotic patients (12, 25). Most pharmacological therapies used to reduce portal pressure are based on the reduction of portal flow and HVPG is used to monitor drug efficacy (2, 6, 9, 20). Indeed, it has been demonstrated that both HVPG and drug-induced reduction in HVPG are excellent predictors of survival and development of complications in
patients with cirrhosis (2, 6, 9, 10, 20, 27, 28).

Data showing the influence of hepatic arterial blood flow on the HVPG in patients with cirrhosis are limited. In fact, these data are controversial and the influence from hepatic arterial blood flow on the HVPG is difficult to conclude from these studies (23, 24). However, most of these studies compared baseline hepatic arterial blood flow and HVPG whereas the influence of changes in hepatic arterial flow on HVPG has not been investigated. Using intravascular Doppler sonography it has been shown that adenosine-induced hepatic arterial vasodilation leads to an increase in HVPG (15). Although this was investigated only in a small number of cirrhotic patients it suggested a direct influence of changes in hepatic arterial flow on HVPG. However, the above-described concept of measuring drug efficacy using HVPG assumes no significant contribution from the hepatic arterial flow to portal venous pressure and hepatic venous wedge pressure (16, 29, 30). Therefore, the aim of this study was to investigate the influence of different hepatic arterial and portal venous flows on wedged and portal pressure.

Methods

Twenty-two control and cirrhotic male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) underwent in situ liver perfusion. The American Physiological Society guide principles for the care and use of animals were followed. The appropriate Institutional Animal Care and Use committee previously approved all procedures involving animals.
Induction of cirrhosis

Rats weighing 75-100 g underwent inhalation exposure of CCl₄ three times a week. Phenobarbital (0.35 g/l) was added to the drinking water as described previously (19). Treatment was given for approximately 14 weeks. Perfusions were performed 6 to 10 days after the last doses of CCl₄ and Phenobarbital. Age-matched rats were used as a control group.

In vivo measurement of portal pressure

Rats were weighed and anaesthetized with ketamine hydrochloride (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA; 100 mg/kg body wt) and diazepam (10 mg/kg body wt). Before each experiment, all pressure measurement systems were calibrated with the zero point at the level of the hepatic hilium. The abdomen was opened with a midline incision and the ileocolic vein was cannulated. After a 10-minute stabilization period the in vivo portal venous pressure was measured. Portal hypertension was defined by a portal pressure higher than 10 mmHg (1).

In situ rat liver perfusion

After measurement of the portal pressure in vivo xylazine (Rompum, Bayer, Shawne Mission, KS; 40 mg/animal) was added and an in situ bivascular liver perfusion via the portal vein and the hepatic artery was performed as previously described (7). Briefly, the opening of the abdomen was extended and loose
ligatures were placed around the aorta cranial of the celiac artery, around the mesenteric artery immediately after branching from the aorta, and the aorta caudal of the mesenteric artery. Left gastric and splenic arteries were tied at its origin of the celiac artery. Left and right renal arteries as well as gastroduodenal artery (branch of the common hepatic artery) were ligated. The bile duct was cannulated with a polyethylene tube (PE 10). Loose ligatures were placed around the inferior vena cava and the portal vein. The portal vein was cannulated with a 14-gauge Teflon catheter and the perfusion with 32 ml/min of oxygenated (carbon gas, 95% O₂, 5% CO₂) Krebs-Henseleit solution containing dextrose (11mM) in a non-recirculating mode was started. The inferior vena cava was cut immediately. The ligatures around the portal vein were closed. The aorta was cannulated with an 18-gauge Teflon catheter and the ligature around the mesenteric artery was closed. The perfusion of the hepatic artery with 8 ml/min of oxygenated (carbon gas, 95% O₂, 5% CO₂) Krebs-Henseleit solution containing dextrose (11mM) in a non-recirculating mode was started. The tip of the catheter was placed close to the branch of the celiac artery and all ligatures around the aorta were closed. A 14-gauge catheter was introduced in the inferior vena cava and the thorax was opened.

In order to measure the sinusoidal pressure, a PE-60 catheter was guided from the right atrium, through the thoracic segment of the inferior vena cava into the left hepatic lobe and wedged in the hepatic vein. The ligature around the superior vena cava was closed to secure the wedged catheter. The preparation was transferred to a temperature-controlled (37° Celsius) Plexiglas perfusion chamber.
Zipprich: Role of hepatic artery on wedged pressure

(Yale University Medical Instrument). The perfusion system was changed to a recirculating mode (100 ml Krebs-Henseleit solution containing dextrose) initiating the stabilization period.

During the stabilization and the experimental period the perfusion pressure of the portal vein (PVPP) and the hepatic artery (HAPP) were measured constantly using two independent strain-gauge transducers (P23XL, Spectramed, Oxnard, CA), respectively. The wedged pressure (WP) was measured during the experimental period using a third independent strain-gauge transducers (P23XL, Spectramed, Oxnard, CA). The free hepatic venous pressure was taken as zero in the outflow of the perfusion system, which allows us to use the WP as a continuous measurement and also as a proof of a wedged position during the entire experiment since a non-wedged position measurement would be closer to the zero reference point. Before each experiment, all pressure measurement systems were calibrated with the zero point at the level of the hepatic hilium. Perfusion and sinusoidal pressure were continuously recorded by Chart 3.6 program using MacLab/4e hardware (AD instruments). During the stabilization and experimental period the perfusate was oxygenated using a Silastic tubing lung interposed between the perfusate reservoir and the peristaltic pump (13).

Experimental design

Normal and cirrhotic livers were perfused with constant flows during the stabilization period and the flow through the wedged catheter was maintained. After the stabilization period the wedged catheter outflow was interrupted to allow
the measurement of the WP. During Experiment 1 the initial portal venous flow (PVF) of 32 ml/min was reduced 2 ml/min every 2 min to a final flow of 20 ml/min. Next PVF was reset to 32 ml/min initiating a second 15-minute period of stabilization. After this second stabilization period (Experiment 2) the hepatic arterial flow (HAF) was first reduced from 8 ml/min to 5 ml/min and then increased to 10 and 15 ml/min with a 2-minute interval between flows.

Portal venous vascular resistance (PVR) and hepatic arterial vascular resistance (HAR) were calculated by portal venous perfusion pressure and portal venous flow and by hepatic arterial perfusion pressure and hepatic arterial flow, respectively. Sinusoidal vascular resistance (SVR) was calculated by wedge pressure and by total liver perfusion flow, i.e. the sum of portal venous and hepatic arterial flow.

Liver global viability was assessed by gross appearance of the liver, stable perfusion pressure and bile production during the stabilization periods (>0.4 µl/min per g liver). After the experiment liver and spleen were removed and weighed. Liver tissue samples were collected and fixed in formalin.

Statistic

Data are presented as mean ± SEM. Mann-Whitney test was used for comparisons of different groups at baseline level. Comparison for repeated measurements was assessed using Friedman-Test to detect changes in each group (within group effects). Multivariate analysis of repeated measurements (ANOVA) was used to detect differences between control and cirrhotic groups.
(between group effect). The association between continuous variables was assessed with the Spearman rank correlation. P-values ≤ 0.05 were considered significant.

Results

In vivo portal pressure

Cirrhosis was confirmed by histological examination in all CCl₄-treated animals (n=9). Cirrhotic animals (12.4±0.8 mmHg) had a significantly higher in vivo portal pressure than control animals (6.6±1.0 mmHg; p<0.001). Body weight was not different between cirrhotic (449±9.6 g) and control (474±12.8 g; n=13) animals while ratios of liver weight and spleen weight to body weight were higher in cirrhotic animals (p<0.05).

Experiment 1

Change of portal venous flow

The decrease of portal venous flow induced an increase of sinusoidal vascular resistance in cirrhotic (p<0.001) as well as control (p<0.001) animals. Furthermore, this decrease of portal venous flow correlated with the flow-induced increase of sinusoidal vascular resistance in cirrhotic (r=-0.63, p<0.001) as well as in control (r=-0.52, p<0.001) animals. However, this observed increase of sinusoidal vascular resistance was not significantly different between both groups. Decrease of portal venous flow did not lead to significant changes of hepatic arterial perfusion pressure in both groups.
Changes of portal venous vascular resistance

Decrease of portal venous flow caused significant changes of portal venous perfusion pressure and portal venous vascular resistance in cirrhotic (p<0.001) and control (p<0.001) animals but without significant differences between both groups.

Flow-induced changes of portal venous perfusion pressure correlated with changes of wedged pressure in cirrhotic animals (r=0.75, p<0.001). Furthermore, changes of portal venous vascular resistance correlated well with changes of sinusoidal vascular resistance in cirrhotic animals (r=0.92, p<0.001, figure 1) and in control animals (r=0.67, p<0.001).

Experiment 2

Change in hepatic arterial flow

Changes of hepatic arterial flow lead to significant changes of portal venous perfusion pressure and portal venous vascular resistance (p<0.01; figure 2). The changes of hepatic arterial flow were, in addition, correlated with changes of portal venous perfusion pressure as well as portal venous vascular resistance in cirrhotic (r=0.64, p<0.001) and in control (r=0.66, p<0.001) animals. Interestingly, we also observed changes of wedged pressure due to changes in hepatic arterial flow. Changes in hepatic arterial flow caused changes of wedged pressure and sinusoidal vascular resistance in cirrhotic and control animals (p<0.01; figures 2). Moreover, we found a correlation between changes of hepatic arterial flow and
changes of wedged pressure in both groups (cirrhosis: \( r=0.71 \), \( p<0.001 \); control: \( r=0.82 \), \( p<0.001 \)). However, changes of portal venous perfusion pressure, portal venous vascular resistance, wedged pressure, and sinusoidal vascular resistance were not significant different between cirrhotic and control animals due to changes of hepatic arterial flow (Figure 2). Although there may be a trend to have different slopes between normal and cirrhotic livers, the slopes shown in Figure 2 are not statistically different. Interestingly, the changes of portal venous perfusion pressure and wedged pressure in response to changes of hepatic arterial flow were highly correlated in both groups (cirrhosis: \( r=0.92 \), \( p<0.001 \), figure 3; control: \( r=0.77 \), \( p<0.001 \)).

Change in hepatic arterial vascular resistance

In response to changes of hepatic arterial flow cirrhotic animals had significantly smaller changes of hepatic arterial perfusion pressure (15.7±0.8 vs. 20.6±1.3 mmHg; ANOVA: \( p=0.01 \)) and hepatic arterial vascular resistance (-2.71±0.06 vs. -3.17±0.19 mmHg\(\cdot\)ml\(^{-1}\)\cdot\)min\(^{-1}\); \( p=0.03 \)) than control animals. In cirrhotic animals, changes of hepatic arterial perfusion pressure correlated to changes of portal venous perfusion pressure (\( r=0.60 \), \( p=0.001 \)) and wedged pressure (\( r=0.72 \), \( p<0.001 \)). In addition, changes of hepatic arterial resistance correlated with changes of portal venous vascular resistance (\( r=-0.66 \), \( p<0.001 \)) and sinusoidal vascular resistance (\( r=0.58 \), \( p=0.002 \)) in cirrhotic animals. These correlation where also present in control animals (portal venous perfusion pressure: \( r=0.66 \),
Comparison of Experiment 1 and 2

To estimate the effect of portal venous flow with the effect of hepatic arterial flow on wedged pressure we compared the results from Experiment 1, reduction of portal venous flow, with the results from Experiment 2, reduction of hepatic arterial flow. Interestingly, changes of wedged pressure and sinusoidal vascular resistance were similar in response to reduction of PVF or to reduction of HAF.

Discussion

The hepatic venous wedged pressure gives an excellent approximation to actual portal pressure and is used to monitor the effect of drug efficacy in portal hypertension (2, 12, 20). Moreover, at the moment, it is the only method that can define the portal pressure response to pharmacological therapy, since other clinical or radiological parameters do not reliably reflect this response (12). However, this concept of measuring drug efficacy using HVPG assumes that the decrease achieved on portal pressure and hepatic venous wedged pressure is all mediated by a decrease of portal venous inflow (16, 29, 30).

In the present study we show a significant influence of hepatic arterial flow on portal venous and wedged pressure as well as portal venous resistance and sinusoidal resistance in cirrhotic and normal animals. Moreover, we found a correlation between flow-induced changes of portal venous perfusion pressure.
and wedged pressure due to both changes in portal venous as well as hepatic arterial flow. Several studies have shown an excellent correlation between portal venous and hepatic venous wedged pressure in animals as well as in humans (11, 12, 21).

In our study portal venous perfusion pressure correlated well with the wedged pressure due to changes in portal venous as well as hepatic arterial flow. Animal studies investigating the influence of hepatic arterial flow on portal venous pressure found different results. Decreasing or stopping hepatic arterial flow modifies the portal venous pressure over a wide range (3, 8, 14, 22). Reduction in hepatic arterial flow caused decreases in portal venous pressure probably due to alterations in total blood flow through the sinusoids (3, 22). However, all of these studies were performed in normal animals and did not measure the sinusoidal resistance. Our study was performed in both cirrhotic and normal animals and we measured the wedged pressure, a reflection of sinusoidal resistance. We found that changes of portal venous pressure and resistance in response to decreased and increased hepatic arterial flows were similar in cirrhotic and control animals. Our results with equal changes in sinusoidal resistance in both models support the hypothesis that alteration in total blood flow through the sinusoids is the main mechanism of changes in portal resistance. Furthermore, the same response on wedged pressure and sinusoidal resistance following changes in flow either in the portal vein or in the hepatic artery support this hypothesis. Moreover, it indicates that in the liver perfusion model the portal venous vascular resistance is located in the sinusoids (3). On
the other hand, changes in hepatic arterial flow were smaller in cirrhotic animals. Smaller increases in hepatic arterial flow caused equal increases in wedged pressure when compared cirrhotic to control livers. This could be interpreted as a greater influence of hepatic arterial flow on wedged pressure in cirrhosis.

In cirrhotic animals as well as in patients, hepatic arterial vascular resistance has been shown to be higher than, equal to or lower than that without liver disease (5, 15, 23, 26, 30, 32, 33). We found a significant less increase in hepatic arterial pressure in CCl₄-induced cirrhotic compared to normal animals in response to increase in hepatic arterial flow. The mechanisms involved in this vasodilatation have not been completely elucidated but it has been shown that the hepatic artery is under local as well as systemic influence (15, 17). Therefore, an involvement of different locally and systemically produced vasodilatatory factors like nitric oxide and adenosine are possible (4, 32).

To investigate the influence of the hepatic arterial flow on portal venous as well as wedged pressure we used a bivascular liver perfusion system. Although this preparation is established since years there are some differences to in vivo measurements. The viscosity of the Krebs-Heinseleit solution is lower than the viscosity of blood, which leads to a lower shear stress and subsequent to a lower perfusion pressure and vascular resistance. Furthermore, we could not observe a change of hepatic arterial vascular resistance due to changes of portal venous perfusion flow. Therefore, it seems that this preparation lacks the hepatic arterial buffer response. It was described from other investigators that the perfusion system does not show the normal hepatic arterial buffer response (3). However,
in preliminary experiments (data not shown) with a greater decrease of portal venous flow we found a marked decrease of hepatic arterial vascular resistance showing the presence of the hepatic arterial buffer response in the used perfusion system.

In conclusion, this study demonstrates that changes in hepatic arterial flow lead to respective changes in portal venous and wedged pressure. Our findings indicating a direct influence of hepatic arterial flow on portal venous and wedged pressure most likely due to changes in total flow through the sinusoids. This was observed in cirrhotic as well as in normal animals and a similar reduction of portal venous and hepatic arterial flow lead to comparable reduction in wedged pressure.

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References:


Figure 1
Correlation between absolute changes of portal venous vascular resistance (PVR) and sinusoidal resistance (SVR) in cirrhotic animals due to changes in portal venous flow ($r=0.92$, $p<0.001$)

Figure 2
Relative changes of wedge pressure (WP; left panel) and portal venous perfusion pressure (PVPP; right panel) due to different hepatic arterial flows in cirrhotic (solid line; $n=9$) and control (pointed line; $n=13$) animals (within-group effect: *$p<0.001$, $\times p=0.002$). Error bars indicate ±1 SEM.

Figure 3
Correlation between absolute changes of portal venous perfusion pressure (PVPP) and wedge pressure (WP) in cirrhotic animals due to changes in hepatic arterial flow ($r=0.92$, $p<0.001$)
<table>
<thead>
<tr>
<th>ΔPVF [ml/min]</th>
<th>ΔPVPP [mmHg]</th>
<th>ΔHAPP [mmHg]</th>
<th>ΔWP [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Δ% total perfusion flow [%])</td>
<td>(Δ%PVPP [%])</td>
<td>(Δ%HAPP [%])</td>
<td>(Δ%WP [%])</td>
</tr>
<tr>
<td>-2 Control</td>
<td>-0.22±0.02</td>
<td>0.12±0.10</td>
<td>-0.08±0.04</td>
</tr>
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<td>(-5) Cirrhosis</td>
<td>-0.21±0.06</td>
<td>-0.02±0.70</td>
<td>-0.11±0.04</td>
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<td>0.32±0.34</td>
<td>-0.13±0.07</td>
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<td>(-10) Cirrhosis</td>
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<td>-0.15±0.11</td>
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<td>0.64±0.54</td>
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<td>-0.65±0.11</td>
<td>-0.18±0.16</td>
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<tr>
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<td>(-20) Cirrhosis</td>
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<td>-0.18±0.16</td>
<td>-0.37±0.14</td>
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<tr>
<td>-10 Control</td>
<td>-1.02±0.06</td>
<td>1.12±0.91</td>
<td>-0.29±0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhosis</td>
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<tr>
<td>(-25)</td>
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<td>-1.03±0.15</td>
<td>-0.10±0.14</td>
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<td></td>
<td></td>
<td>(-15.27±2.07)</td>
<td>(-0.15±0.22)</td>
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<tr>
<td>-12</td>
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<td>-1.24±0.07</td>
<td>1.22±0.91</td>
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<td></td>
<td></td>
<td>(-19.10±1.05)</td>
<td>(1.15±0.78)</td>
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<tr>
<td>(-30)</td>
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<td>0.003±0.16</td>
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<td></td>
<td></td>
<td>(-18.83±1.97)</td>
<td>(0.02±0.24)</td>
</tr>
</tbody>
</table>
Table 1

Legend: Absolute (Δ) and relative (Δ%) changes in portal venous perfusion pressure (PVPP), hepatic arterial perfusion pressure (HAPP), and wedged pressure (WP) due to changes in portal vein flow (PVF; Experiment 1)

PVPP (Control and Cirrhosis): p<0.001 (within-group effect)

WP: Control p=0.002 (within-group effect); Cirrhosis p=0.025 (within-group effect)
### Table 2

<table>
<thead>
<tr>
<th>ΔHAF [ml*min⁻¹] (Δ% total flow [%])</th>
<th>ΔPVPP [mmHg] (Δ%PVPP [%])</th>
<th>ΔHAPP [mmHg] (Δ%HAPP [%])</th>
<th>ΔWP [mmHg] (Δ%WP [%])</th>
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</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-3 (-7.5)</td>
<td>-0.10±0.03 (-1.4±0.4)</td>
<td>-10.5±0.74 (-13.4±0.3)</td>
<td>-0.18±0.03 (-7.1±1.3)</td>
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<tr>
<td><strong>Cirrhosis</strong></td>
<td>-0.14±0.06 (-1.93±0.86)</td>
<td>-7.93±0.30 (-12.28±0.20)</td>
<td>-0.19±0.07 (-5.00±1.64)</td>
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<tr>
<td><strong>Control</strong></td>
<td>+0.06±0.05 (+0.8±0.6)</td>
<td>+6.7±0.45 (+8.5±0.3)</td>
<td>+0.12±0.04 (+4.1±1.3)</td>
</tr>
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<td>+2 (+5)</td>
<td>+0.06±0.09 (+1.14±0.98)</td>
<td>+5.12±0.26 (+7.92±0.25)</td>
<td>+0.07±0.09 (+2.71±1.31)</td>
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<tr>
<td><strong>Control</strong></td>
<td>+0.19±0.08 (+2.6±1.0)</td>
<td>+20.6±1.25 (+26.4±0.6)</td>
<td>+0.40±0.10 (+14.8±2.7)</td>
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<td>+7 (+17.5)</td>
<td>+0.28±0.11 (+4.10±1.33)</td>
<td>+15.70±0.76 (+24.27±0.63)</td>
<td>+0.32±0.11 (+9.64±2.34)</td>
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</table>

**Legend:** Absolute (Δ) and relative (Δ%) changes in portal vein perfusion pressure (PVPP), hepatic arterial perfusion pressure (HAPP), and wedged pressure (WP) due to changes in hepatic arterial flow (HAF; Experiment 2)

HAPP: p<0.001 (within-group effect); p=0.01 (ANOVA cirrhosis vs. control, between-group effect)
PVPP: $p \leq 0.002$ (within-group effect)

WP: $p < 0.001$ (within-group effect)
Figure 1

![Graph showing the relationship between absolute change in SVR (mmHg/ml/min) and absolute change in PVR (mmHg/ml/min).](image-url)
Figure 2

![Graph showing the relationship between hepatic arterial flow (ml/min) and relative change in WP and PVPP (%). The graph includes error bars indicating variability.]
Figure 3