Hepatic artery buffer response following left portal vein ligation: its role in liver tissue homeostasis

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Rocheleau, B., C. Éthier, R. Houle, P. M. Huet, and M. Bilodeau. Hepatic artery buffer response following left portal vein ligation: its role in liver tissue homeostasis. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G1000–G1007, 1999.—Occlusion of a lobar portal vein is known to induce atrophy of downstream liver lobes and hypertrophy of contralateral lobes. Changes in portal flow are known to be compensated by changes in hepatic arterial flow, thus defining the hepatic artery buffer response (HABR). To understand the role of liver flow in liver atrophy, we measured portal flow and hepatic artery flow after different degrees of left portal vein stenosis (LPVS). Surgery was performed to obtain 0, 43, 48, 59, 68, 72, 78, and 100% LPVS. Systemic and splanchnic blood flows were measured at 4 h or 7 days after surgery using radiolabeled microspheres. At 4 h, LPVS produced no changes in systemic hemodynamics. Increasing degrees of LPVS produced a significant decrease in left portal flow ($P < 0.0001$) and a fully compensatory increase in right portal flow ($P < 0.0001$) without significantly affecting total portal flow. Left hepatic artery flow increased by $210\%$ ($P = 0.002$), and right hepatic artery flow decreased by $67\%$ ($P = 0.05$) after full LPVS. There was a significant inverse correlation between portal and arterial flow changes induced by different degrees of LPVS in the left ($r^2 = 0.61$) and right ($r^2 = 0.41$) lobes. Despite this HABR, we observed a reduction in left liver flow ($-45\%$, $P = 0.01$) and an increase in right liver flow ($+230\%$, $P = 0.01$) with 100% LPVS. At 7 days, a significant decrease in the weight of left liver lobes ($-75\%$, $P < 0.0001$) and a compensatory increase in the weight of the right lobes ($+210\%$, $P < 0.0001$) were observed with 100% LPVS. Left and right liver flows were similar to results measured at 4 h, and HABR was still present. However, when expressed per gram of liver, liver flows were identical to results obtained with sham animals. Reduction in lobar portal flow is accompanied by an increase in ipsilateral hepatic artery flow and a compensatory increase in portal flow to the rest of the liver. In a given lobe, when compensatory HABR is overcome, liver weight changes occur so that at the end total liver flow per gram of liver tissue is restored. This suggests that in normal conditions liver flow is a major regulator of liver volume.

liver flow; liver atrophy; liver regeneration

STENOSIS OF THE MAIN portal vein is a model of portal hypertension in the rat (3). This experiment is also known to induce mild liver atrophy. The effects of the ligation of a branch of the portal vein on portal pressure are controversial (24, 25); however, it has been shown to produce severe atrophy of the liver irrigated by the ligated portal vein branch and compensatory hypertrophy of the residual liver lobes (22, 23). We have previously shown that the atrophy induced by this operation is caused by liver cell loss through apoptosis and necrosis and that the severity of the atrophy and of the injury was correlated with the degree of portal vein branch stenosis (1).

The mechanisms leading to cell death and liver atrophy of the ligated lobes and to hypertrophy of the nonligated ones are not known. Because the stimulus is to produce a reduction in portal flow, it is tempting to hypothesize that the decrease in portal flow is the primary force leading to these changes. This would lead to hypoxemia of the liver distal to the ligation as well as to deprivation of portal hepatotrophic factors that are thought to be important for liver cell survival and proliferation (5, 6).

The liver is well known to have a dual flow, delivered by the portal vein and the hepatic artery, with 75% of the total flow coming from the portal vein and 25% from the hepatic artery (9, 18). Portal flow can vary significantly in response to a wide variety of stimuli, such as the feeding state (4). However, there is no evidence so far that the liver can directly control portal flow. The only control of flow within the liver comes from the hepatic artery (11). Changes in arterial pressure lead to inverse changes in arterial flow, thus defining the classic arterial autoregulation phenomenon. Extrinsic humoral regulation of the hepatic artery has also been shown to occur (11). Interestingly, changes in portal flow have been shown to affect the flow of the hepatic artery. When total portal flow is reduced, there is a rapid increase in the flow of the hepatic artery (11). Conversely, an increase in portal flow leads to a reduction in arterial flow. This phenomenon is known as the hepatic artery buffer response (HABR). Several authors have investigated the physiology of this response, and it is actually postulated that the variations of flow observed are due to the degree of clearance of an intrahepatic arterial vasodilator (adenosine) to which the hepatic artery is very sensitive (14). Indeed, adenosine has been shown to be a potent vasodilator of the hepatic artery (13). When portal flow is decreased, the concentration of adenosine is thought to increase because of less washout, thus resulting in arterial dilation. The exact location of the synthesis and stockage of adenosine is not known, but it is postulated to be into the space of Mall, which is the zone surrounding the hepatic arterial resistance vessels and portal venules (10).

In this paper, we describe the hemodynamic changes occurring in the liver after different degrees of left portal vein stenosis. Flows were assessed by radiolabeled microsphere determination. We describe observa-
tions strengthening the physiological concept of the
HABR in that context and demonstrating the impor-
tance of liver flow in the regulation of liver cell mass.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats (Charles River Labor-
atories, St. Constant, PQ) weighing 175–200 g were used for
these studies. After a 2-day period of acclimatization, surgery
was performed between 9:00 AM and 12:00 PM. Animals
received humane care and had access to food and water ad
libitum. The experiments described in this report were con-
ducted according to the Guide for the Care and Use of
Laboratory Animals published by the National Institutes
of Health (Bethesda, MD). The experimental protocol has
also been reviewed and approved by the animal care committee
of Hôpital Saint-Luc, Montréal.

Portal vein ligation. Animals were operated as described
previously (1). Briefly, under gas anesthesia (N\textsubscript{2}O\textsubscript{2} 2:1, 1.5%
isoﬂurane), a midline abdominal incision was performed
and the left portal vein was carefully separated from the left bile
duct and hepatic artery. Sham surgery and 100% stenosis
were performed; 43, 48, 59, 68, 72, and 78% stenosis of the left
portal vein were also induced with the use of graded needles.
The same needle was reused for every animal of the same
group of stenosis to obtain a reliable degree of similarity.
The degree of stenosis obtained with these needles has been
described previously (1). The abdominal wall was closed, and
the animals were watched until full awakening.

Hemodynamic measurements. Under gas anesthesia with
isoﬂurane (which is known not to affect splanchnic microcircu-
lation and to maintain HABR (19)), polyethylene catheters
were inserted in the right femoral artery, the left carotid
artery down to the left ventricle, and the femoral vein up to
the inferior vena cava. Finally, a catheter was inserted, after
abdominal incision, in the main portal vein from a distal
puncture in the inferior mesenteric vein. All cannulas
were ﬁlled with heparinized saline (1,000 IU/ml). The position of
the ventricular catheter was veriﬁed by recognition of ven-
tricular pressure tracing, which was recorded directly, to-
gether with arterial, caval, and portal pressures, on a multi-
channel direct-writing polygraph. The pressure-measurement
catheters were calibrated against water columns equivalent
to 0, 10, 20, and 30 mmHg.

The reference withdrawal method was applied to measure
blood ﬂows (8,17). We used standard carbonized micro-
spheres with mean diameters of 15.5 ± 1 μm labeled with
\textsuperscript{141}Ce and \textsuperscript{85}Sr (DuPont NEN, Boston, MA). For systemic flow,
70,000 cpm \textsuperscript{85}Sr-labeled microspheres were injected in a
volume of 100 μl in a flush in the left ventricle. The total
radioactivity of the microspheres was determined in a gamma
counter before injection. An arterial reference sample was
withdrawn at a constant rate from the femoral artery using a
Harvard pump (0.79 ml/min). Withdrawal started 15 s before
microsphere injection and continued for a total of 75 s. Homogeneous microsphere distribution was veriﬁed postmor-
tem by comparing the left and right renal cpm values. For
portal flow distribution, a bolus of 50,000 cpm \textsuperscript{141}Ce-labeled
microspheres in a volume of 200 μl was injected in the main
portal vein (upstream from the ligation and 4 cm away from
the bifurcation of the left and right portal veins to obtain
adequate mixing in the portal vein) after systemic blood ﬂow
measurements and just before euthanasia. The respective
\textsuperscript{141}Ce-speciﬁc radioactivity recovered in different liver lobes
was measured. Total portal ﬂow was calculated as the sum of
all the different splanchnic organ ﬂows.

Experimental protocol. In a ﬁrst set of experiments, the
acute effect of left portal vein stenosis (LPVS) was studied.
Different degrees of stenosis were performed in three animals
each. Animals were then left to recuperate from surgery and
to fully awaken. Three hours later, they were reanesthetized
in order to place the vascular catheter for the microsphere study.
Hemodynamic studies were performed 4 h after the LPVS
surgery, because a preliminary study had shown a sudden
increase in the main portal pressure after a 100% LPVS that
had largely subsided after 4 h (data not shown).

In the second experiment, two groups of animals (n = 3)
that had undergone sham operation and 100% LPVS were
studied to determine the weight of the left and right liver
lobes 4 h and 1, 2, 3, 7, and 10 days after surgery. The weight
of the different parts of the liver was measured after expul-
sion of blood by gentle compression with gauze.

In the last experiment, sham-operated and 100% LPVS
animals (n = 5) underwent liver blood flow measurements at
4 h and 7 days after surgery. In both groups, animals were left
to awake after LPVS before a subsequent and final anesthe-
sia was performed for the hemodynamic studies.

Statistics. All results are expressed as means ± SE.
Statistical analysis was performed by ANOVA with the
Tukey’s method for posttest comparisons. Correlation coefﬁ-
cients were performed using the Spearman coefﬁcient method.
A P value <0.05 was considered signiﬁcant.

RESULTS

Effect of left portal vein stenosis on liver hemodynamics
at 4 h. The left portal vein was ligated to obtain 0,
43, 48, 59, 68, 72, 78, or 100% stenosis. Four hours
later, cardiac output, splanchnic regional blood ﬂows,
and left and right portal ﬂow proportions were mea-
sured with the use of radiolabeled microspheres in-
jected in the left ventricle and in the main portal vein
as described in MATERIALS AND METHODS.

In sham-operated animals, after anesthesia, resting
blood pressure was 82 ± 7 mm Hg, cardiac output was
27 ± 3 ml·min\textsuperscript{-1}·100 g body wt\textsuperscript{-1}, and caval pressure
was 0.5 ± 0.3 mm Hg. Systemic hemodynamics were
not affected by stenosis of the left portal vein (Table 1).
There were no signiﬁcant differences in the weight of
the liver due to the stenosis; when the left and right
lobes were analyzed separately, there were still no
signiﬁcant differences (data not shown).

There were also no signiﬁcant changes in the portal
pressure and in total portal ﬂow (Table 1). Total liver
flow signiﬁcantly increased with LPVS (P = 0.019); this
was due to an increase in the hepatic artery ﬂow (P
(0.007).

Because there were no signiﬁcant changes in total
portal ﬂow, we looked at the respective left and right
portal ﬂows by dividing the total portal ﬂow by the
proportion of ﬂow delivered to the left and right lobes,
respectively, as measured with \textsuperscript{141}Ce microspheres
injected in the main portal vein. In sham animals, 67% of
total portal ﬂow goes to the left lobes. Figure 1A shows
that there was a signiﬁcant decrease in the left portal
flow, which started at 48% LPVS and became worse up
to 100% LPVS. Conversely, the right portal ﬂow in-
creased in a manner that mimicked the changes in left
portal ﬂow. The capacity of the right lobes to accommo-
date for the totality of the portal ﬂow (which was not
Table 1. Effect of different degrees of LPVS on systemic and liver hemodynamics

<table>
<thead>
<tr>
<th>Group, %LPVS</th>
<th>BP, mmHg</th>
<th>CO, ml·min⁻¹·100 g⁻¹</th>
<th>CP, mmHg</th>
<th>PP, mmHg</th>
<th>TPF, ml·min⁻¹·g⁻¹</th>
<th>TAF, ml·min⁻¹·g⁻¹</th>
<th>TLF, ml·min⁻¹·g⁻¹</th>
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<tbody>
<tr>
<td>0</td>
<td>82 ± 7</td>
<td>27 ± 3</td>
<td>0.5 ± 0.3</td>
<td>6.7 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>1.2 ± 0.2</td>
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<tr>
<td>43</td>
<td>96 ± 1</td>
<td>25 ± 3</td>
<td>0.7 ± 0.2</td>
<td>10.9 ± 3.0</td>
<td>0.8 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>1.2 ± 0.3</td>
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<tr>
<td>48</td>
<td>91 ± 4</td>
<td>26 ± 2</td>
<td>0.8 ± 0.3</td>
<td>8.1 ± 0.5</td>
<td>0.9 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>59</td>
<td>88 ± 7</td>
<td>24 ± 4</td>
<td>0.6 ± 0.5</td>
<td>7.1 ± 0.4</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1*</td>
<td>1.0 ± 0.3†</td>
</tr>
<tr>
<td>68</td>
<td>92 ± 3</td>
<td>29 ± 2</td>
<td>0.8 ± 0.3</td>
<td>7.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.1*</td>
<td>1.5 ± 0.1†</td>
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<tr>
<td>72</td>
<td>91 ± 5</td>
<td>24 ± 1</td>
<td>0.5 ± 0.2</td>
<td>8.3 ± 0.7</td>
<td>0.8 ± 0.1</td>
<td>0.6 ± 0.1*</td>
<td>1.5 ± 0.1†</td>
</tr>
<tr>
<td>78</td>
<td>94 ± 7</td>
<td>26 ± 2</td>
<td>0.8 ± 0.2</td>
<td>7.6 ± 0.4</td>
<td>0.7 ± 0.1</td>
<td>0.4 ± 0.1*</td>
<td>1.2 ± 0.2†</td>
</tr>
<tr>
<td>100</td>
<td>89 ± 7</td>
<td>22 ± 1</td>
<td>0.6 ± 0.4</td>
<td>8.5 ± 0.3</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1*</td>
<td>1.4 ± 0.1†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Measurements were performed 4 h after left portal vein stenosis (LPVS). Mean blood pressure (BP) and caval pressure (CP) were measured with transducers. Cardiac output (CO) was measured by the reference sample microsphere method. Portal pressure (PP), total portal flow (TPF), and total liver arterial flow (TAF) were measured with radiolabeled microspheres. Total liver flow (TLF) was estimated as the sum of TPF and TAF. *P < 0.0007, †P = 0.02. All other results were not significant.

On examination of the hepatic arterial flow, we also observed that 67% of the total hepatic artery flow is delivered to the left lobes in sham animals. Because the two portal and arterial ratios are determined independently and with a different method, this similarity strengthens the reliability of our observations. Figure 1B shows that, after ligation of the left portal vein, there was a reciprocal change in the arterial flow of the left and right lobes of the liver. However, contrary to what was observed with portal flow, the arterial flow significantly decreased in the right lobes and increased in the left lobes. At 100% LPVS, 90% of the total hepatic arterial flow was directed toward the left lobes. Between sham and 100% LPVS, arterial flows decreased by 0.68 ml/min in the right lobes, whereas it increased by 6.97 ml/min in the left lobes. This resulted in a net increase in the total arterial flow as already observed in Table 1.

Table 2. Effect of different degrees of LPVS on the proportion of liver flow afforded by the portal vein and the hepatic artery in left and right liver lobes

<table>
<thead>
<tr>
<th>Group, %LPVS</th>
<th>LPF, %LHF</th>
<th>RPF, %RHF</th>
<th>LAF, %LHF</th>
<th>RAF, %RHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78 ± 6</td>
<td>78 ± 6</td>
<td>21 ± 6</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>43</td>
<td>73 ± 4</td>
<td>87 ± 2</td>
<td>26 ± 4</td>
<td>12 ± 2</td>
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<tr>
<td>48</td>
<td>77 ± 3</td>
<td>86 ± 6</td>
<td>22 ± 3</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>59</td>
<td>56 ± 6</td>
<td>83 ± 6</td>
<td>43 ± 6</td>
<td>16 ± 6</td>
</tr>
<tr>
<td>68</td>
<td>22 ± 6</td>
<td>96 ± 2</td>
<td>77 ± 6</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>72</td>
<td>23 ± 3</td>
<td>95 ± 2</td>
<td>76 ± 3</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>78</td>
<td>14 ± 4</td>
<td>96 ± 2</td>
<td>85 ± 4</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>100</td>
<td>0 ± 1</td>
<td>96 ± 3</td>
<td>99 ± 1</td>
<td>3 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. Measurements were performed 4 h after surgery with the radiolabeled microsphere method. LPF, left portal flow; LHF, left hepatic flow; RPF, right portal flow; RHF, right hepatic flow; LAF, left hepatic artery flow; RAF, right hepatic artery flow. P < 0.0001 for all measurements.

Fig. 1. Effect of left portal vein stenosis (LPVS) on lobar portal flows (A) and hepatic arterial flows (B). Liver flows were measured 4 h after sham operation or at 43, 48, 59, 68, 72, 78, and 100% degrees of LPVS. Measurements were made with radiolabeled microspheres as described in MATERIALS AND METHODS, and each point is mean ± SE of 3 independent experiments.
accounted for 21% of the total hepatic flow in sham animals, represented up to 99% of this flow in the left lobes of 100% LPVS animals. When animals from different degrees of ligation were analyzed, there was a significant inverse correlation between portal and arterial flows in both lobes ($r^2 = 0.61$ and 0.41 for left and right lobes, respectively) (Figs. 2A and 2B). However, these responses did not lead to full restoration of the flow irrigating liver lobes; with increasing degrees of LPVS, we could observe a significant increase ($P = 0.0002$) in the flow delivered to the right lobes as well as a significant decrease in the flow to the left lobes ($P = 0.001$) (Fig. 3). At 100% LPVS, there was a 45% reduction in left liver flow ($P = 0.01$) and a 230% increase in right liver flow ($P = 0.01$). In the same condition, the proportion of compensation from the HABR ($\Delta$hepatic artery flow/$\Delta$portal flow $\times 100$) was calculated to be 44% in the left lobes and 10% in the right lobes.

Effect of left portal vein ligation on lobar liver weights. Because LPVS is known to induce atrophy of the left lobes, we hypothesized that it was the flow variations observed early after surgery that would determine the variations in the amount of liver tissue. We recorded the weight of the liver in sham-operated and 100% LPVS animals at 4 h and 1, 2, 3, 7, and 10 days after surgery. We observed no significant differences in the total weight of the liver (data not shown). On the other hand, when the weight of the right and left lobes were analyzed separately, there was a gradual and very severe loss in left liver weight in 100% LPVS animals in comparison with sham-operated animals (−75%, $P < 0.0001$) (Fig. 4A). A reciprocal increase in the weight of the right lobes was observed (+210%, $P < 0.0001$) (Fig. 4B). At 7 days, changes in liver mass were nearly maximal.

![Figure 2. Correlations between lobar arterial and portal liver flows in animals subjected to different degrees of LPVS. Arterial and portal flow measures in each animal were correlated in left (A) and right (B) liver lobes. Correlation coefficients were measured with the Spearman method.](image)

![Figure 3. Effect of LPVS on total lobar flows in left (A) and right (B) liver lobes. Flows were measured at 4 h after sham operation or at 43, 48, 59, 68, 72, 78, and 100% LPVS.](image)
Liver hemodynamics 7 days after left portal vein ligation. We then hypothesized that liver flow, through its regulatory mechanism (which includes the HABR), is a determinant of residual liver volume in our model. If this held true, we would observe a return toward normal values in total hepatic flow (per gram of liver tissue) delivered to the left and right lobes after completion of the volume changes. In the last experiment, liver flows were recorded in sham-operated and 100% LPVS animals 4 h and 7 days after surgery, the latter point being chosen as the new steady state of the liver weight.

Table 3 shows that no differences could be observed in total liver flow, total portal flow, or arterial flow between the four groups. However, when the flows were analyzed in the left and right lobes separately, there were significant increases in total hepatic flow going to the right lobe at 4 h and 7 days after ligation. A decrease in the left flows was also observed. When flows were now expressed per gram of liver weight, the difference observed at 4 h was absent at 7 days. The right and left flows 7 days after a 100% LPVS were very similar to the ones observed in sham-operated animals.

When portal flow was measured in the right lobes, a 246% increase in flow was observed 4 h after 100% LPVS. At 7 days, due to the hypertrophy of the right lobes, the difference subsided when the results were analyzed per gram of liver weight. Similarly, the arterial flow delivered to the left lobes was marginally increased 4 h after surgery, but, expressed per gram of liver tissue, it increased by more than 666% at 7 days. Thus, through the sole perfusion of the hepatic artery, the remnant left side liver lobes were perfused with flow rates similar to the right lobes, which were perfused via both the portal vein and the hepatic artery.

DISCUSSION

The experiments performed in this study were aimed at evaluating the consequences of ligation of one branch of the portal vein on liver blood flows and, more specifically, on the response of the hepatic artery to changes induced in lobar portal flows. The impact of these flow changes on liver mass was also evaluated. We did not observe durable effects of LPVS on portal pressure in our model. In a preliminary study, a modest increase in portal pressure occurred just after surgery, but this quickly returned toward normal values so that no difference between sham-operated and 100% LPVS groups could be observed when the portal pressure was measured 4 h after LPVS surgery. Consequently, we did not observe significant alterations in systemic hemodynamics in our model. This observation is in contradiction to the results of Um et al. (25), who performed similar studies to ours but claimed that 100% LPVS is a model of portal hypertension similar to partial stenosis of the main portal vein. We cannot explain the difference between their results and ours, except that their surgical maneuver excluded 80% of the liver from portal flow, whereas 66% of liver is excluded in our model with 100% LPVS. There is no evidence that portal hypertension is steadily induced in our model because portal pressures that were measured in animals studied 7 days after surgery were again not increased (6.8 ± 0.8 mmHg). Our results are in accord with those of Siman et al. (24). They did not identify increase in portal pressure after 100% LPVS in dogs, whereas such an increase was found after partial hepatectomy.

The results presented show that total portal flow is not affected by experimental modification in portal flow to one branch of the portal vein. This suggests that splanchnic blood flow is not regulated by local intrahepatic resistance in normal conditions. Indeed, to accommodate the increase in flow to the right lobes, intrahepatic portal resistances to the right lobes had to decrease significantly. This is probably due to a high degree of distensibility of portal vein as already described by Lautt and Légaré (12).
Our results show that it is necessary to induce a significant degree of stenosis (>60%) before observing significant changes in ipsilateral portal flow and hence reciprocal changes in arterial flow. This is somewhat surprising because our degree of stenosis is estimated as the percentage of reduction of the diameter of the vein. We think that this observation is possibly explained by the high degree of distensibility of portal vessels (12). As such, the upstream portal vein might serve as a capacitance vessel and enable flow to occur at the same rate across a short stenosis. The anatomy of the left portal vein, which is in the same axis as the main portal vein (whereas the right portal vein bifurcates at a 90° angle from the main portal vein) (1), might also favor the maintenance of flow toward left liver lobes more easily than diversion toward the right lobes.

On the other hand, the changes in portal flow induced in each liver lobe had significant impact on the flow of the hepatic artery. Globally, there was a slight increase in the arterial flow to the liver. This result is surprising because no changes in total portal flow were observed. However, it could have been due to surgical manipulations. The decrease in left portal flow was accompanied by a major increase in the arterial flow to the left lobes that made up for a decrease in the arterial flow to the right lobes. These changes in arterial flow occur in response, and are proportional, to the flow changes observed in lobar portal flow. Therefore, they can be regarded as a true hepatic artery buffer response as has been described previously in other models (13, 15). The interest of our model as far as the HABR is concerned is that the response occurs in a setting of steady cardiac output, portal pressure, and total portal flow and that opposing responses are observed in the same animal. It is of interest that the compensation afforded by the HABR was different in each liver lobe. The increase in left arterial flow was much more potent than the decrease in right arterial flow in buffering portal flow changes. This can be easily understood because the resting arterial flow is modest and can only be decreased to a certain limit. The increase in total liver arterial flow is an argument to understand that arterial flow changes should not be viewed as a theft of flow from one side to the other but as an intact and independent response to ipsilateral portal flow changes.

The net changes in total liver flow to each liver lobe strongly suggested to us that the atrophy/hypertrophy observed in liver lobes in this model were linked with the hemodynamic changes produced. Indeed, when liver flows were measured at a period where the changes in liver mass were almost complete, there was a restitution in the proportion of flow (as expressed per gram of liver tissue) delivered to each lobe. Because arterial and portal flows were not significantly different from what had been measured at 4 h when expressed in

<table>
<thead>
<tr>
<th>Liver Flows</th>
<th>Sham (4 h)</th>
<th>Sham (7 days)</th>
<th>LPVS (4 h)</th>
<th>LPVS (7 days)</th>
</tr>
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<tbody>
<tr>
<td>Total liver flow</td>
<td>13.3 ± 1.3</td>
<td>16.7 ± 2.5</td>
<td>14.6 ± 1.5</td>
<td>14.6 ± 2.8</td>
</tr>
<tr>
<td>ml/min</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Portal flow</td>
<td>10.2 ± 1.3</td>
<td>13.3 ± 2.3</td>
<td>9.9 ± 1.0</td>
<td>11.0 ± 1.7</td>
</tr>
<tr>
<td>ml/min</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.1</td>
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</tr>
<tr>
<td>Arterial flow</td>
<td>3.0 ± 0.4</td>
<td>3.3 ± 0.8</td>
<td>4.6 ± 0.7</td>
<td>3.6 ± 1.3</td>
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<tr>
<td>ml/min</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.3 ± 0.2</td>
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<tr>
<td>Total left liver flow</td>
<td>9.1 ± 1.0*</td>
<td>11.1 ± 1.9†</td>
<td>4.4 ± 0.7*</td>
<td>2.7 ± 0.8†</td>
</tr>
<tr>
<td>ml/min</td>
<td>1.6 ± 0.2‡</td>
<td>1.6 ± 0.3 (NS)</td>
<td>0.7 ± 0.2‡</td>
<td>2.1 ± 0.7 (NS)</td>
</tr>
<tr>
<td>Left portal flow</td>
<td>7.0 ± 0.9</td>
<td>8.7 ± 1.8</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>ml/min</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>Left arterial flow</td>
<td>2.0 ± 0.3</td>
<td>2.3 ± 0.6</td>
<td>4.4 ± 0.7</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>ml/min</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td>Total right liver flow</td>
<td>4.1 ± 0.4*</td>
<td>5.6 ± 0.8†</td>
<td>10.1 ± 0.9*</td>
<td>10.9 ± 1.5†</td>
</tr>
<tr>
<td>ml/min</td>
<td>1.5 ± 0.2‡</td>
<td>1.7 ± 0.2 (NS)</td>
<td>3.5 ± 0.4‡</td>
<td>1.3 ± 0.2 (NS)</td>
</tr>
<tr>
<td>Right portal flow</td>
<td>3.1 ± 0.5</td>
<td>4.5 ± 0.8</td>
<td>9.9 ± 1.0</td>
<td>10.3 ± 1.4</td>
</tr>
<tr>
<td>ml/min</td>
<td>1.2 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>3.4 ± 0.4</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Right arterial flow</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>0.2 ± 0.1</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>ml/min</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Results are expressed as crude flows (ml/min) and relative to tissue weight (ml·min⁻¹·g⁻¹). Respective shares of total liver flow from portal and arterial vessels are also depicted. *, †, and ‡ P < 0.05 between sham-operated and 100%-LPVS groups. NS, not significant.
absolute numbers, this result suggests that both portal and arterial flows can maintain viable liver mass in proportion to the amount of flow being delivered. However, the comparative architecture and functional capacities of these two differently irrigated liver tissues need to be addressed.

The results described in this report are in agreement with the HABR described by Lautt et al. (10, 11). Furthermore, they confirm the observations of others (7, 25) that 1) the HABR can take place regionally inside the liver and that 2) opposing responses can be observed in the same animal. Our results show a strong correlation between portal and arterial flows whatever the direction of changes in portal flow. They also confirm that the degree of compensation from the hepatic artery is only partial. These changes occur without significantly affecting systemic hemodynamic or portal pressure as measured 4 h after LPVS. The dual response observed in both liver lobes in our model is consistent with the hypothesis that it is the washout of a vasoactive substance (adenosine) present in liver acini that is responsible for the arterial flow changes. However, our data have not directly tested the hypothesis that it is the washout of adenosine that governs the HABR. Changes in the quality of the blood delivered to the liver parenchyma (O2 content or saturation, vasoactive hormones, growth factors) or changes in the vessel tone (shear stress, production of nitric oxide) could be other etiologic factors that would fit with the arterial consequences that occur after changes in portal flow on either side of the liver. Nevertheless, based on the adenosine washout hypothesis, by decreasing portal flow to the left lobes, less adenosine would be washed away, leading to a vasodilatory response of the left hepatic artery. In the right lobes, adenosine would be more efficiently cleared, thus leading to a local vasoconstriction of the right hepatic artery. The results also suggest that the regulation in hepatic arterial flow is not systemic in nature because it occurs independently in both lobes.

This is the first time that the HABR is also shown to have a potential physiological role different from the autoregulation of liver flow. The observation of a major increase in arterial flow delivered to the left lobes and the subsequent return to normal flow as expressed per gram of liver tissue suggests that, if the HABR had not occurred, the left lobe remnant would have completely disappeared due to flow insufficiency. It is tempting to extrapolate this observation to clinical situations in which there is an abrupt cessation of the portal flow (portocaval shunts, transjugular intrahepatic shunts) that should be compensated by an increase in arterial flow to maintain liver mass. In support of this hypothesis, it has been shown that the liver becomes arterialized after portocaval shunts (2, 16, 21). Platt et al. (20) have also shown a decrease in hepatic arterial resistance (an indirect evidence of increased flow) in the context of portal vein thrombosis.

The relationship between liver flow and liver mass delineated in this study suggests that some factor present in both arterial and portal flows or driven by such flows is in part responsible for the maintenance of the liver cell mass. This factor(s) remains to be identified. The role of oxygen delivery, which is partly correlated with flow rates, will need to be addressed. Humoral factors such as insulin, growth factors, adenosine, and catecholamines are also potential agents that could influence liver cell mass.

This study has defined the acute and long-term hemodynamic consequences of LPVS in the rat. It confirmed the HABR already described in other models but extends these observations to regional differences inside the liver, differences that are strongly associated with changes in the liver mass. This study also shows the usefulness of this model in evaluating potential factors involved in the maintenance of tissue homeostasis inside the liver.

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