

# Arterialization of the portal vein improves hepatic microcirculation and tissue oxygenation in experimental cirrhosis

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**Background:** Arterialization of the portal vein (APV) has shown beneficial effects on liver regeneration and function in selected patients undergoing liver resection and transplantation. Whether APV improves liver perfusion and function in cirrhosis is unclear. This study investigated the effect of APV on hepatic haemodynamics and liver function in a rat model of cirrhosis.

**Methods:** Male Sprague–Dawley rats (250–300 g) were divided into three groups: normal controls ( $n = 7$ ), cirrhosis with sham laparotomy (sham;  $n = 7$ ) and cirrhosis with APV (APV;  $n = 9$ ). Portal venous blood flow, portal vein pressure and hepatic parenchymal microcirculation (HPM) were measured before and after APV. Hepatic parenchymal oxygenation was assessed by near-infrared spectroscopy and hepatocellular injury by standard liver function tests. Measurements were taken at baseline, after APV and 7 days after surgery.

**Results:** APV increased portal blood flow and pressure in cirrhotic rats without altering intrahepatic portal resistance. APV increased the HPM in cirrhotic rats by a mean (s.e.m.) of 28.5(0.1) per cent on day 0 and 54.6(0.1) per cent by day 7 ( $P = 0.001$ ). Liver tissue oxygenation was increased by APV and the plasma  $\gamma$ -glutamyltranspeptidase level was reduced (mean (s.e.m.) 6.0(0.5) versus 3.8(0.3) units/l before and after APV respectively;  $P = 0.006$ ) at day 7.

**Conclusion:** APV increases portal blood flow, tissue perfusion and oxygenation in cirrhosis.

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## Introduction

End-stage cirrhosis is the most common indication for liver transplantation and accounts for approximately 80 per cent of cases worldwide<sup>1</sup>. However, owing to the substantial resources required for transplantation, only 1 per cent of patients with cirrhosis have the opportunity to be treated by this option. Other effective strategies for the treatment for liver cirrhosis are required.

The liver is perfused uniquely by both systemic arterial and portal venous blood from the splanchnic circulation. The total flow and contribution from arterial and portal sources depends on resistance to flow. During cirrhosis, there is a reduction in portal inflow because of increased intrahepatic resistance<sup>2</sup>, which leads to impaired hepatic parenchymal microcirculation (HPM)

and parenchymal dysfunction. This might be improved by augmentation of portal inflow using a mechanical pump<sup>3,4</sup> or shunting well oxygenated and high-pressure arterial blood into the portal circulation. Mechanical enhancement of portal venous inflow in animal models and human cirrhosis improves HPM, tissue oxygenation and hepatocellular function<sup>3–5</sup>, but long-term safety, reliability and biocompatibility of implantable mechanical pumps must be established.

Arterialization of the portal vein (APV) has been used to reduce the risk of liver failure after total portacaval shunting<sup>6</sup> and is an alternative approach to enhancing portal blood flow in cirrhosis. Hepatic arterial blood flow (HABF) increases after insertion of a portacaval shunt in patients with cirrhosis and portal hypertension, and increased arterial flow is directly associated with

reduced morbidity and mortality rates and improved long-term survival<sup>7</sup>. APV has been used in both human and experimental liver surgery<sup>8–10</sup> and transplantation<sup>11,12</sup>. In rats that underwent extended hepatectomy, hepatic energy metabolism and liver regeneration was significantly improved after APV<sup>10</sup>, and APV improved the survival of patients with portal vein thrombosis who had liver transplantation<sup>12</sup>. The role of APV in patients with portal vein thrombosis requires clarification<sup>13</sup>.

The effect of APV on hepatic haemodynamics and liver function in cirrhosis has not been investigated. The present study was designed to investigate the effects of APV, established by direct anastomosis of a hepatic artery and portal vein branch, on hepatic haemodynamics and liver function in a rat model of liver cirrhosis.

## Materials and methods

### Animal preparation and surgical procedures

The study was conducted under a licence granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. Male Sprague–Dawley rats weighing between 250 and 300 g were used. Liver cirrhosis was induced with 0.03 per cent thioacetamide (Sigma Chemical, Poole, UK) added to drinking water for 12 weeks<sup>14</sup>. Control animals had free access to tap water. Both groups had free access to normal diet. Bodyweight of the animals was monitored weekly.

After induction of cirrhosis, the rats were anaesthetized using 1.5–2.0 per cent isoflurane in oxygen and nitrous oxide (1:2) using a face mask in a standard anaesthetic circuit. The body temperature of the animals was maintained at 36–38°C by means of a heating pad (Harvard Apparatus, Edenbridge, UK) with temperature monitored rectally. The arterial oxygen saturation and heart rate were monitored continuously using a pulse oximeter (Ohmeda Biox 3740-pulse oximeter; Ohmeda, Louisville, Kentucky, USA) throughout the experiment. PE-50 polyethylene catheters (Portex, Hythe, UK) were inserted into the right femoral artery and connected to a pressure transducer for monitoring of mean systemic arterial blood pressure, and in the right femoral vein for administering normal saline (1 ml per 100 g bodyweight per h) to compensate for intraoperative blood loss. The abdomen was opened through a midline incision and the liver was exposed. The gastroduodenal artery and vein were dissected. Atraumatic clamps were applied to parallel segments of both vessels and longitudinal incisions were made on the anterior wall of both vessels. An arteriovenous shunt was formed by side-to-side anastomosis using 10/0 polypropylene suture and an operating microscope. The shunt was too short for

placing the transonic Doppler flow probe and successful shunting was therefore determined by measuring the portal venous blood flow (PVBF) before and after completion of the arterioportal shunt. At the second laparotomy, the shunt was cut to confirm its patency. Animals in the sham group underwent the same procedures as those in the APV group but the anastomosis was not performed. The abdomen was closed and animals were allowed to recover from anaesthesia. Animals were allowed free access to fluids and normal diet, and bodyweight was monitored over the first postoperative week. The second laparotomy was carried out under general anaesthesia 7 days after the first laparotomy.

### Assessment of hepatic haemodynamics

A dual transonic flowmeter system (HT207; Transonic Medical, Ithaca, New York, USA) was used for continuous measurement of PVBF and HABF<sup>15</sup>. After dissection and exposure of the hepatic artery and portal vein, perivascular flow probes 1 and 2 mm in diameter were placed around the hepatic artery and portal vein respectively. Portal venous pressure (PVP) and hepatic venous pressure were measured by direct puncture of the portal vein and hepatic vein through liver tissue with a 25-G needle connected to a pressure monitor (Datex-Ohmeda Instrumentarium, Helsinki, Finland). The intrahepatic portal vascular resistance (IHPR) was calculated as PVP/PVBF.

### Measurement of hepatic parenchymal microcirculation

HPM was measured using a commercially available laser Doppler flowmeter (DRT4; Moor Instruments, Axminster, UK). Doppler flowmetry is a non-invasive technique that allows continuous evaluation of microvascular perfusion of the liver; it has been shown previously to be reliable and reproducible<sup>16,17</sup>. The flowmeter probe was placed on a fixed site on the liver and was held in place by a probe holder. The flow in the HPM was expressed in flux units and the values were taken as a mean over a period of 2 min<sup>18</sup>.

### Measurement of hepatic tissue oxygenation

Hepatic tissue oxygenation was measured using near-infrared spectroscopy (NIRS) (NIRO 500; Hamamatsu Photonics, Hamamatsu, Japan) with a computer program developed specifically for measuring hepatic oxyhaemoglobin, deoxyhaemoglobin and cytochrome oxidase in micromoles per litre of tissue<sup>19–21</sup>. A pair of NIRS probes was placed 10 mm apart on the surface of the

liver for monitoring hepatic tissue oxygenation. NIRS was optically initialized to zero at the start of the experiment. NIRS measurements after APV or a sham operation were expressed relative to baseline. The values were obtained as the mean of 2-min recordings.

### Assessment of liver function

The degree of hepatocellular injury was assessed by measurement of plasma concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and  $\gamma$ -glutamyltranspeptidase (GGT) using an automatic biochemical analyser (Hitachi 747; Roche Diagnostics, Lewes, UK).

### Experimental protocols

Animals were divided randomly into control ( $n = 7$ ) and cirrhosis ( $n = 16$ ) groups. Cirrhotic animals were further divided into APV ( $n = 9$ ) and sham-operated (sham;  $n = 7$ ) groups. After laparotomy, systemic and hepatic haemodynamic data were recorded as baseline in all groups. Immediately after completion of APV or sham operation (day 0), the haemodynamic variables were measured again. The anaesthetic was then reversed and animals recovered. Second laparotomy was carried out 7 days later and haemodynamic measurements were repeated. Blood samples were taken intraoperatively before and after APV (day 0) and 7 days after the first laparotomy for the assessment of liver function. Animals were killed by exsanguination under anaesthesia. Livers and spleens were removed immediately and weighed. Their wet weights were calculated relative to bodyweight. Liver samples were subjected to histological examination.

### Histological examination

Liver tissue specimens were fixed in 10 per cent formalin solution and embedded in paraffin. The tissue sections were stained with haematoxylin and eosin, and examined under a light microscope by a pathologist who had no knowledge of the treatment. Typical histological characteristics of cirrhosis were defined as bridging fibrosis, loss of normal lobular architecture and macronodular regeneration.

### Data collection and statistical analysis

The output from the transonic flowmeter system, laser Doppler flowmeter, blood pressure monitor and pulse oximeter, together with NIRS data, were fed into a laptop personal computer. The systemic haemodynamic

data were fed into a commercially available analogue-to-digital data acquisition recording system (MacLab<sup>®</sup>; AD Instruments, Hastings, UK). During the experiments, hepatic and systemic haemodynamic data were monitored continuously at a rate of 1 Hz. All haemodynamic data were averaged over 2 min at each observation. Values were expressed as mean(s.e.m.). One-way ANOVA with Bonferroni correction was used unless stated otherwise. Student's *t* test was used for statistical analysis between the groups.  $P < 0.050$  was considered statistically significant.

## Results

### Animal model and arterialization of the portal vein

Liver cirrhosis developed in all animals with 12 weeks of thioacetamide administration. Ascites was noted at the time of surgery in five of 16 animals. The liver was enlarged with macronodular cirrhosis and there was splenomegaly (Table 1). Histologically, the livers showed marked fibrosis and regenerative nodules, with an appearance resembling human liver cirrhosis.

The systemic and hepatic haemodynamic variables in cirrhotic animals are shown in Table 2. Mean systemic arterial blood pressure was significantly lower in cirrhotic rats than in controls ( $P = 0.001$ ). There was a 30.0(0.5) per cent reduction in PVBF in cirrhotic rats compared with controls ( $P = 0.002$ ). In contrast to PVBF, HAPBF was increased by 66.7(0.4) per cent in cirrhotic rats ( $P = 0.006$ ). IHPR was significantly increased in cirrhotic rats in comparison to control animals ( $P < 0.001$ ) and flow in the HPM was significantly reduced (31.8(0.8) per cent;  $P = 0.001$ ).

APV was achieved successfully within 30 min by anastomosis between the gastroduodenal artery and vein without interruption of hepatic inflow. All animals recovered from anaesthesia and resumed a normal diet until further anaesthesia on day 7. There was no significant loss in bodyweight after APV or sham operation by postoperative day 7 (426.6(5.3) versus 414.4(6.3) g in the APV group and 423.5(5.3) versus 414.6(6.3) g in the sham group;  $P = 0.158$  and  $P = 0.301$  respectively).

**Table 1** Bodyweight, and liver and spleen weights in control and cirrhotic rats

	Control	Cirrhosis	<i>P</i> †
No. of rats	7	16	
Bodyweight (g)	445.0(2.9)	482.0(30.1)	0.432
Liver weight (g per kg BW)	32.5(0.5)	70.6(2.3)	< 0.001
Spleen weight (g per kg BW)	1.3(0.1)	3.1(0.5)	< 0.008

Values are mean(s.e.m.). BW, bodyweight. †Unpaired Student's *t* test.

**Table 2** Basic characteristics of systemic and hepatic haemodynamics observed in thioacetamide-induced cirrhosis and changes after arterialization of the portal vein

	Cirrhosis						
	Control	Sham			APV		
		Baseline	Day 0	Day 7	Baseline	Day 0	Day 7
MAP (mmHg)	87.3(2.1)	74.4(1.6)†	75.5(2.3)	77.5(1.8)	75.3(1.4)†	72.4(1.3)	73.8(1.7)
HR (beats/min)	243.9(0.9)	224.8(0.2)	244.7(0.2)	244.9(0.1)	244.4(0.2)	238.7(5.9)	244.1(0.7)
SaO <sub>2</sub> (%)	98.0(2.0)	97.0(1.2)	95.7(1.3)	96.6(0.8)	95(1.0)	96.0(0.0)	98.5(1.5)
HABF (ml/min)	3.6(0.6)	6.0(0.3)†	5.7(0.3)	—	6.4(1.0)†	5.8(0.2)	—
PVBF (ml/min)	12.0(0.7)	8.4(0.3)†	8.3(0.4)	8.5(0.6)	9.2(0.2)†	11.3(0.5)§**	11.7(0.4)¶††
PVP (mmHg)	6.5(0.4)	9.4(0.2)‡	9.8(0.2)	9.6(0.2)	9.1(0.2)‡	11.0(0.4)	11.3(1.1)
HVP (mmHg)	2.8(0.2)	3.0(0.3)	2.6(0.2)	2.6(0.2)	2.8(0.4)	2.1(0.1)	2.4(0.2)
IHPR (mmHg/min/ml)	0.6(0.0)	1.0(0.0)*	1.1(0.1)	1.0(0.1)	1.0(0.0)*	1.0(0.1)	0.9(0.1)
HPM (flux units)	141(7)	97(6)†	88(10)	108(9)	96(8)†	121(6)§	145(7)§

Values are mean(s.e.m.). APV, arterialization of the portal vein; MAP, mean systemic arterial blood pressure; HR, heart rate; SaO<sub>2</sub>, oxygen saturation; HABF, hepatic arterial blood flow; PVBF, portal venous blood flow; PVP, portal venous pressure; HVP, hepatic vein pressure; IHPR, intrahepatic portal resistance; HPM, hepatic parenchymal microcirculation. \**P* < 0.050, †*P* < 0.010, ‡*P* < 0.001 versus control; §*P* < 0.010, ¶*P* < 0.001 versus baseline; \*\**P* = 0.001 versus sham day 0; ††*P* = 0.001 versus sham day 7 (one-way ANOVA).

There were no major operative complications. Abdominal adhesions were present in all animals. One animal that had undergone APV developed jaundice and was found to have a bile duct injury at the second laparotomy. A contained bile collection was found within dense abdominal adhesions. This complication made hepatic haemodynamic assessment impossible during the second laparotomy, so this animal was excluded from subsequent analysis. Exposure of the portal vein and arteriovenous shunt at reoperation was difficult owing to adhesions. The arteriovenous shunt was patent in eight of nine animals 7 days after formation of the anastomosis; the shunt arterial flow was 2.4(0.3) ml/min (*n* = 8) in comparison to a hepatic arterial flow of 5.8(0.2) ml/min.

**Effect of arterialization of the portal vein on systemic and hepatic haemodynamics**

Changes in systemic and hepatic haemodynamics following APV are summarized in Table 2. There were no significant changes in mean arterial blood pressure and heart rate. PVBF and PVP were significantly increased in cirrhotic rats immediately after APV (day 0) and at postoperative day 7. PVBF and PVP remained unchanged in cirrhotic rats after sham operation. HPM was significantly improved after APV in cirrhotic animals by 28.5(0.1) per cent at day 0 and 54.6(0.1) per cent at day 7 (*P* = 0.001 versus sham).

**Effect of arterialization of the portal vein on hepatic tissue oxygenation**

Changes in hepatic tissue oxygenation in cirrhotic rats after APV or sham operation are shown in Table 3. Hepatic

tissue oxyhaemoglobin and cytochrome oxidase levels were significantly higher in rats that underwent APV (relative to baseline) compared with levels in sham-operated rats at both day 0 and day 7, in parallel with the improvement in HPM.

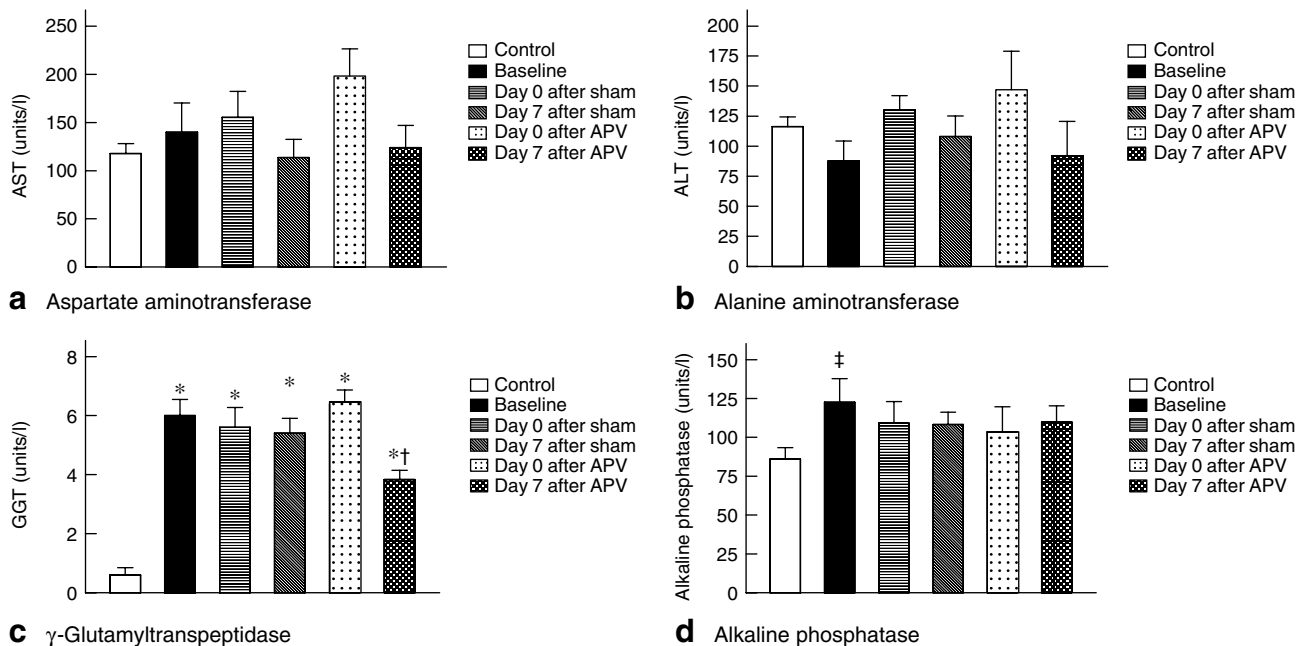
**Effect of arterialization of the portal vein on hepatocellular injury**

There were no significant differences in plasma AST and ALT between control and cirrhotic rats. Levels of GGT and alkaline phosphatase were increased significantly in cirrhotic rats compared with levels in controls (*P* < 0.001). After APV, AST and ALT levels in cirrhotic animals were raised on day 0 but returned to baseline by day 7. GGT

**Table 3** Changes in hepatic tissue oxygenation according to the baseline after arterialization of the portal vein or sham operation in cirrhotic rats

	Sham		APV	
	Day 0	Day 7	Day 0	Day 7
Deoxyhaemoglobin (µmol/l)	-27.3(7.3)	22.8(24.9)	22.6(19.0)	39.9(29.8)
Oxyhaemoglobin (µmol/l)	-76.0(17.1)	-145.9(21.7)	73.3(28.0)*	12.9(25.1)‡
Cytochrome oxidase (µmol/l)	-4.0(1.7)	-3.0(1.6)	12.4(2.4)†	5.2(1.6)§

Values are mean(s.e.m.). APV, arterialization of the portal vein. \**P* = 0.001, †*P* < 0.001 versus sham day 0; ‡*P* = 0.004, §*P* = 0.003 versus sham day 7 (Student's *t* test).



**Fig. 1** Mean (s.e.m.) levels of liver enzymes **a** aspartate aminotransferase (AST), **b** alanine aminotransferase (ALT), **c**  $\gamma$ -glutamyltranspeptidase (GGT) and **d** alkaline phosphatase before and after arterialization of the portal vein (APV). Baseline, values before APV. \* $P < 0.001$  versus control; † $P = 0.006$  versus control; ‡ $P = 0.043$  versus baseline (one-way ANOVA)

levels in cirrhotic animals decreased after APV ( $P = 0.006$ ) (Fig. 1).

### Histology

The livers of thioacetamide-treated animals showed marked fibrosis and regenerative nodules. There were no significant morphological changes in the liver 1 week after APV or sham operation.

### Discussion

Well described experimental models of hepatic cirrhosis include bile duct ligation<sup>22</sup>, and administration of carbon tetrachloride<sup>23</sup> or thioacetamide<sup>24,25</sup>. All have been used for the study of hepatic haemodynamics associated with cirrhotic portal hypertension. However, the thioacetamide-induced model of cirrhosis used in this study most closely resembles human cirrhosis<sup>25</sup>. The cirrhotic rats in this study showed decreased mean systemic arterial blood pressure and PVBF whereas PVP and IHPR increased, and the HPM was reduced. These hepatic haemodynamics are typical of cirrhosis. HABF was increased in cirrhotic rats compared with that in control animals. This might represent a protective effect to maintain parenchymal perfusion in response to the reduced

portal inflow of cirrhosis through the mechanism of the hepatic arterial buffer response<sup>26</sup>. Clamping the portal vein decreased sinusoidal perfusion by only 9.5 per cent in animals with partial portal vein ligation, in contrast to 71.2 per cent in sham-operated animals<sup>27</sup>. The liver may maintain its microcirculatory flow by vascular remodelling from the hepatic arterial vasculature.

In the present study, APV was performed by surgical anastomosis between a branch of the hepatic artery and portal vein. Although this technique has been reported previously in large animals such as dogs<sup>9</sup>, it has not been used in small experimental models because of technical difficulties. APV has been applied in a rat model of extended hepatectomy<sup>10</sup>, but the arteriovenous shunt was formed between the proximal end of the ligated hepatic artery and a branch of the portal vein using a polyethylene tube and not direct anastomosis. Therefore normal hepatic arterial flow was interrupted and total liver blood flow was not increased. A synthetic conduit is unlikely to be suitable for long-term studies because of shunt occlusion. In the present study, the arteriovenous shunt was established between a branch of the hepatic artery and the portal vein, leaving a patent hepatic artery and avoiding liver inflow occlusion during anastomosis. A direct surgical arteriportal anastomosis has a good chance of long-term patency; indeed, only one shunt occluded in the present study. This model may therefore

be appropriate for long-term studies. One clinical study of arterioportal shunting demonstrated patency at 5 years<sup>28</sup>.

Of the limited studies that have evaluated haemodynamic and functional changes following APV<sup>8–12</sup> none has determined the optimal shunt volume. Fibrosis of the liver after liver transplantation in humans has been reported following total APV. This may be a consequence of high-pressure portal blood flow or right heart decompensation due to volume overload<sup>11</sup>.

In the present study, there were increases in liver AST and ALT levels immediately after APV in comparison to levels in the sham group. As the shunt was performed without hepatic vascular inflow occlusion, the raised enzyme levels may be related to the stress of the surgical procedure and liver handling rather than ischaemia. AST, ALT and GGT are markers of hepatocellular injury rather than liver function. Clearance studies using galactose, lidocaine or indocyanine green would be required to assess functional changes<sup>29,30</sup>.

The short-term effects of APV in normal liver have been reported both in animal models and in humans. In these studies, hepatic energy metabolism and liver viability after APV were critically evaluated<sup>11,31</sup>. In the rat model of extended hepatectomy, APV increased portal blood flow and hepatic parenchymal oxygen supply. Beneficial effects were seen on hepatic energy metabolism, liver regeneration and survival<sup>10</sup>. Only limited data are available on the HPM and tissue oxygenation after APV in normal liver. The effect of APV on hepatic haemodynamics in the cirrhotic liver has not been reported previously. With normal liver blood flow, the liver extracts less than half of the supplied oxygen<sup>32</sup>. In diseased conditions, such as cirrhosis, oxygen demand is increased. Regenerating liver requires an increased amount of oxygen for mitochondrial oxidative phosphorylation to restore hepatic energy charge<sup>33</sup>. Improved liver parenchymal oxygenation may facilitate regeneration and improve parenchymal function. In the present study, hepatic tissue oxygenation was assessed by measurement of concentrations of deoxyhaemoglobin, oxyhaemoglobin and cytochrome oxidase in the hepatic circulation, which represents capillary and intracellular concentrations of oxygen<sup>34,35</sup>. NIRS has been validated extensively for measuring oxygenated and deoxygenated haemoglobin levels, and the redox state of cytochrome oxidase<sup>19,21,36,37</sup>. NIRS allowed the effect of APV on the availability and uptake of oxygen by the hepatic parenchyma to be investigated in the present study. A significant improvement in hepatic oxygenation was observed following APV, especially in intracellular oxygenation indicated by an increase in cytochrome oxidase concentration.

Oxygen utilization by cells occurs promptly via the respiratory chain, located in the inner membrane of the intracellular mitochondria, which comprises a sequence of interlinked, enzyme-controlled reactions<sup>38</sup>. Cytochrome oxidase is one of a superfamily of proteins and acts as the terminal enzyme of the respiratory chain. Its redox state provides a direct indication of intracellular oxidation<sup>38</sup>. A constant supply of oxygen to the tissue is obligatory for production of adenosine 5'-triphosphate (ATP) by oxidative phosphorylation. During hypoxia, when electron transport ceases, the inner membrane potential is developed at the expense of ATP hydrolysis by mitochondrial ATP synthase<sup>39</sup>. An impaired HPM is present in cirrhotic animals. This will decrease uptake of substances, including oxygen, that diffuse to the cells through the sinusoids<sup>40,41</sup>. Thus significant improvement of intracellular oxygenation in cirrhosis after APV may be secondary to an increased flow in the HPM. An improvement in hepatocellular function might also be expected.

Although APV has proved beneficial in maintaining liver perfusion in cirrhosis following a portacaval shunt<sup>6</sup>, the therapeutic role of APV in cirrhosis is uncertain. In the present study APV improved HPM and oxygenation by increasing sinusoidal perfusion but, on the other hand, increased portal inflow and PVP. This might increase the risk of ascites formation and the development of splanchnic collaterals, resulting in variceal bleeding in portal hypertension<sup>42,43</sup>. However, in the present study APV formation was not associated with ascites formation or gastrointestinal bleeding. Whether these develop during long-term observation requires further study. Longer-term studies are also required to evaluate liver function and the effects of the altered hepatic haemodynamics on sinusoidal cell function.

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