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Evaluation of temporary portal vein arterialization: the minimum arterialized blood flow for maintaining liver viability

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Abstract. The effect of temporary portal vein arterialization (PVA) on hepatic energy metabolism was investigated by changes in the arterial blood ketone body ratio (KBR) and hepatic energy charge (EC) level in 17 dogs. The KBR decreased markedly after clamping the hepatic hilar vessels combining mesocaval shunt and remained at a low level throughout hepatic ischemia. After PVA, the KBR was rapidly restored and maintained at sufficient levels. EC at 60 min after arterialization also recovered to the preclamping level. By reducing the arterial shunt flow, the critical point of arterialized blood flow for maintaining the KBR at high levels was assessed to be about 10% of the total hepatic blood flow (THBF). These findings demonstrate that temporary PVA is an effective method for maintaining the functional capacity of the liver, and that the minimum arterialized blood flow needed to preserve liver viability is only about 10% of the total hepatic blood flow.

Key words: Portal vein arterialization – Arterial ketone body ratio – Hepatic energy metabolism

Recently, portal vein arterialization (PVA) has been adopted as a temporary revascularization technique. In liver transplantation, the conventional procedure for vascular reconstruction requires that the suprahepatic inferior vena cava (IVC) anastomosis be performed first, followed by infrahepatic IVC and portal vein anastomoses. Sheil et al. reported a temporary revascularization with arterial blood shunted from the recipient's external iliac artery to the graft portal vein after completion of the suprahepatic IVC anastomosis [18]. The purpose of this method is to minimize the ischemic time for the allograft and the anhepatic period for the recipient, and to perform the anastomoses that follow without the pressure of time contraints. In addition, for the radical operation of bile duct cancer, Mimura et al. proposed a new catheter bypass from the left femoral artery to the umbilical portion of the portal vein to avoid the hepatic ischemia owing to the complete block resection of the hepatoduodenal ligament [13].

Hepatic energy charge (EC) [2] is a valuable parameter for evaluating the viability of the liver [17]. We have reported that the arterial blood ketone body ratio (KBR: acetoacetate/β-hydroxybutyrate), reflecting the hepatic mitochondrial redox state [27], is closely correlated with EC in various kinds of experimental models such as jaundice, hepatectomy, hemorrhagic and endotoxin shock [20, 22, 25, 28]. Consequently, our findings have led us to assert that KBR is the most significant parameter when it comes to evaluating the integrity of hepatic energy metabolism [14]. In fact, KBR has begun to be adopted to assess hepatic function in the medical field and was recently reported to be an early indicator of primary graft failure after liver transplantation [3, 6, 9, 21].

In this study, temporary PVA was evaluated by measuring the KBR and the EC in relation to hepatic energy metabolism, using the canine model first reported by Matzander [11]. In addition, the minimum blood flow of arterialization to maintain the variablity of the liver was evaluated by measurement of the KBR.

Materials and methods

Seventeen mongrel dogs of both sexes, weighing 10–17 kg, were used in this study. The operation was carried out under intravenous administration of ketamine hydrochloride (7 mg/kg) and pancuronium bromide (0.1 mg/kg), using a positive pressure respirator with room air. The left jugular vein was cannulated for intravenous infusion of lactate Ringer's solution (30 ml/kg per hour) and 5% glucose solution (10 ml/kg per hour). The left carotid artery was cannulated for monitoring blood pressure and sampling blood. Blood pressure and

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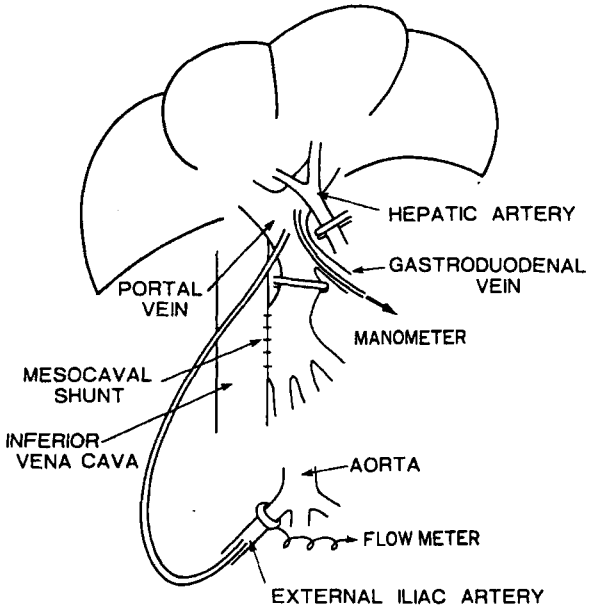

Fig. 1. Schema for portal vein arterialization with a heparin-coated tube shunted from the right external iliac artery to the hepatic side of the portal vein combining mesocaval shunt

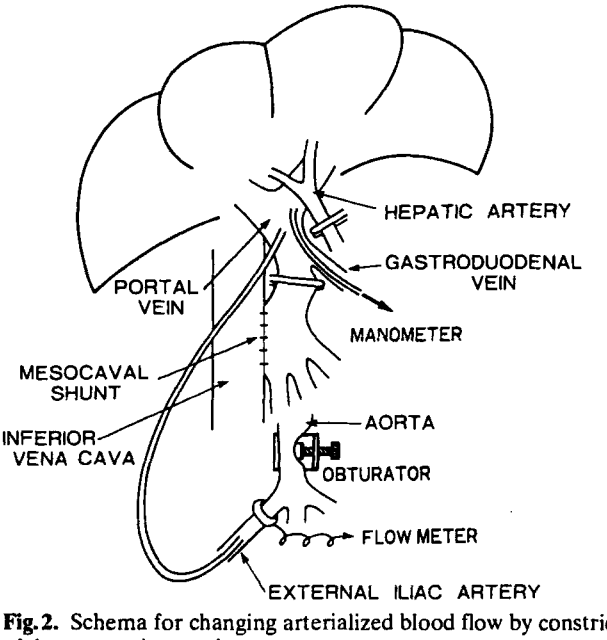

Fig. 2. Schema for changing arterialized blood flow by constriction of the aorta using an obturator

blood sugar were kept at normal levels (> 150 mm Hg and > 150 mg/dl, respectively).

Experiment 1: Hepatic ischemia and portal vein arterialization (n = 10)

After laparotomy, the lesser omentum was ligated and divided from the esophagus to the hepatoduodenal ligament to prevent anastomotic or aberrant inflow into the liver. The common bile duct, hepatic artery, and portal vein were then isolated. A side-to-side mesocaval shunt was performed for splanchnic decompression, followed by ligation of the portal vein and the hepatic artery. Blood samples were taken for measurement of the KBR before and at 5, 15, 30, and 60 min after clamping the hepatic hilar vessels.

The portal vein was arterialized after 60 min of hepatic ischemia by inserting a heparin-coated tube (outer diameter 4 mm, inner diameter 3 mm, length 40 cm) between the right external iliac artery and the hepatic side of the portal vein (Fig. 1). Blood sampling was done at 5, 15, 30, and 60 min after arterialization to measure the KBR.

Portal vein pressure (PVP) was directly monitored by a catheter inserted into the portal vein via the gastroduodenal vein. The catheter was also used to take the portal blood sample for the measurement of oxygen tension (PO_2). Preclamping portal vein flow (PVF), hepatic artery flow (HAF), and blood flow of arterialization were measured using an ultrasonic range-gated pulsed Doppler flow meter designed by Hartley and Cole [4]. The flow probes were placed tightly around the portal vein (probe size 7–8 mm diameter), hepatic artery (3 mm diameter), and right external iliac artery (4–5 mm diameter), which was just proximal to the shunt tube.

Experiment 2: KBR at changed blood flow of arterialization (n = 7)

After blood sampling at 15 min of the portal vein arterialization period, the blood flow of arterialization was reduced by constriction of the aorta using an obturator and was maintained at a certain blood flow level for 15 min for the measurement of the KBR (Fig. 2). The blood flow levels were classified into five groups as follows: 25%, 20%, 12%, 8%, and 0% of preclamping total hepatic blood flow (THBF: PVF + HAF). The blood flow of arterialization without constriction belonged to the 25% group.

Assays of the KBR and hepatic energy charge

Ketone bodies (acetoacetate, β-hydroxybutyrate) in the arterial blood were measured enzymatically, and the KBR was calculated as acetoacetate/β-hydroxybutyrate. About 150 mg of liver tissue was freeze-clamped and prepared for the assay of adenine nucleotides at preclamping time and at 60 min after arterialization. The amounts of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) were measured using high-performance liquid chromatography. Hepatic energy charge levels were calculated according to the formula proposed by Atkinson [2]: (ATP + 1/2ADP)/(ATP + ADP + AMP).

Statistical analysis

All results were expressed as means ± standard error of the mean. Statistical significance was determined by Student's *t*-test, and *P* values less than 0.05 were considered to be significant.

Results

Experiment 1: Hepatic ischemia and portal vein arterialization

Figure 3 shows the changes in the KBR. The KBR decreased immediately from 1.06 ± 0.07 to 0.34 ± 0.07 at 5 min after clamping the hepatic hilar vessels ($P < 0.001$) and remained at a low level throughout hepatic ischemia (0.27 ± 0.07 at 60 min). After arterialization of the portal vein, the KBR rapidly increased and recovered to the pre-

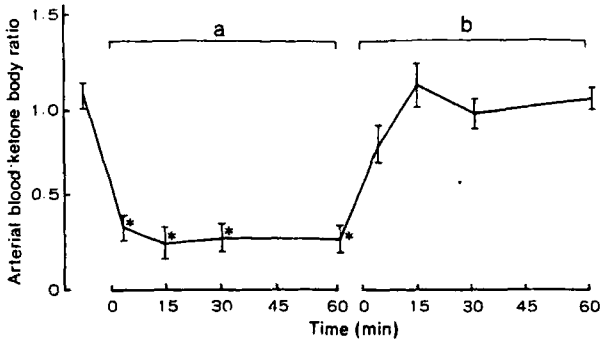

Fig. 3. Changes in the KBR by clamping of hepatic hilar vessels (**a**) and arterialization of the portal vein (**b**) ($n = 10$). Values expressed as means ± SEM. * $P < 0.001$ as compared with preclamping value

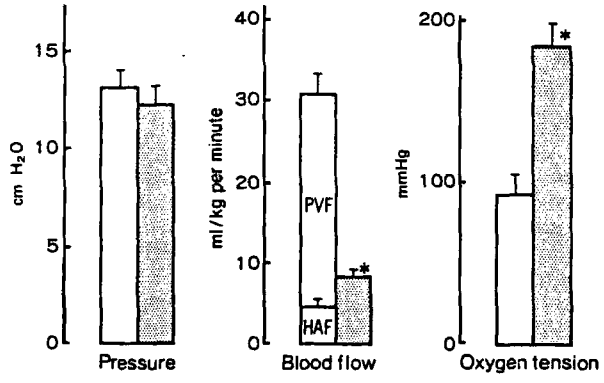

Fig. 4. Portal vein pressure, total hepatic blood flow, and oxygen tension of the blood in the portal vein at preclamping time (□) and at arterialized time (▨) ($n = 10$). Values expressed as means ± SEM. *PVF*, Portal vein flow; *HAF*, hepatic artery flow. * $P < 0.001$ as compared with preclamping value

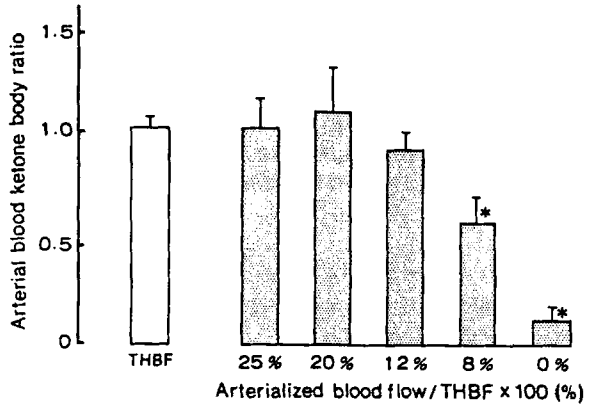

Fig. 5. Levels of the arterial blood ketone body ratio at changed blood flow levels of arterialization ($n = 7$). Values expressed as means ± SEM. *THBF*, preclamping total hepatic blood flow. * $P < 0.01$ as compared with value at THBF. Symbols as for Fig. 5

clamping level within 15 min (1.10 ± 0.12); this level was maintained during arterialization.

The hepatic energy charge level at 60 min after arterialization was 0.865 ± 0.025, which also recovered to the preclamping level (0.870 ± 0.009).

The PVP after arterialization was 12.5 ± 1.0 cm H_2O, which was almost the same as the preclamping value (13.4 ± 0.9 cm H_2O). The preclamping PVF, HAF, and THBF were 26.3 ± 2.2 ml/kg per minute, 4.4 ± 0.8 ml/kg per minute, and 30.7 ± 2.4 ml/kg per minute, respectively. After arterialization, arterialized blood flow was 8.1 ± 0.8 ml/kg per minute, which was significantly less than the preclamping THBF ($P < 0.001$). PO_2 of arterialized portal vein blood was 183.8 ± 11.8 mmHg, which was significantly higher than the preclamping level (91.8 ± 11.8 mmHg; $P < 0.001$; Fig. 4).

Experiment 2: KBR at changed blood flow of arterialization

Figure 5 shows the changes in the KBR at different blood flow levels of arterialization. The KBR at 25% arterialized blood flow was 1.06 ± 0.15, which was almost the same value as the preclamping THBF (1.06 ± 0.06). In spite of reducing the arterialized blood flow from 25% to 12%, the KBR remained almost the same as the value at the preclamping THBF. However, when the arterialized blood flow was reduced to 8% of the preclamping THBF, the KBR decreased significantly to 0.59 ± 0.12 ($P < 0.01$). Finally, the KBR decreased to 0.11 ± 0.07 at 0% blood flow.

Discussion

Portal vein arterialization has been used to prevent an increased risk of hepatic failure following surgical portosystemic shunt for portal hypertension ever since 1952, when Hunt first reported its application in four patients [5]. Many clinical reports and experimental studies have been published that investigate the long-term effects of portal vein arterialization, but the results have not always been good due to anastomotic failure, excessive arterialization, etc. [1, 7, 8, 10, 16, 24, 29].

The effect of temporary PVA on liver function has never been investigated because the procedure had no clinical use and because there were no reliable methods to evaluate such short-term changes. Recently, however, Sheil et al. proposed that the anhepatic period in liver transplantation by temporary PVA be minimized to prevent the induction of anastomotic failure owing to time constraints [19]. Mimura et al. also reported for radical operation of bile duct cancer a new catheter bypass using the same method to avoid hepatic ischemia due to complete block resection of the hepatoduodenal ligament [13]. We, therefore, attempted to evaluate the short-term effect of PVA on hepatic energy metabolism by measuring the KBR.

Acetoacetate and β-hydroxybutyrate are produced in the liver and the ratio of acetoacetate to β-hydroxybutyrate is determined in liver mitochondria by the redox state, which is the ratio of free nicotinamide adenine dinucleotide (NAD^+) to NAD^+ reduced form (NADH), as shown by the following formula [27]: acetoacetate + NADH + H^+ = β-hydroxybutyrate + NAD^+. Since the two ketone bodies freely penetrate the cell membrane, the KBR can be said to reflect the redox state in the liver mitochondria [23]. Citrate synthase, which determines the

turnover rate of the Krebs cycle, is inhibited by the reduced mitochondrial redox potential, as are other enzymatic processes requiring NAD^+ in the mitochondria [26]. Keeping the KBR at the high levels indicative of the normal mitochondrial redox state is essential to maintain the functional capacity of the liver.

In experiment 1, it was demonstrated that the KBR decreased markedly by clamping of the hepatic hilar vessels but could be restored and maintained at sufficient levels by arterialization of the portal vein. Noguchi et al. reported that the KBR decreased immediately after devascularization of the liver and rapidly recovered to the preanhepatic levels following revascularization of both the portal vein and the hepatic artery to the liver [15]. From the viewpoint of changes in the KBR, the effect of arterialization, the blood flow of which was significantly less than the preclamping THBF, is similar to the revascularization of both the portal vein and the hepatic artery. The present data suggest that temporary PVA is a simple and effective method for keeping the high KBR levels necessary for maintaining the functional capacity of the liver. The fact that the hepatic energy charge at 60 min after arterialization recovered to the preclamping level also positively proves the effectiveness of arterialization in relation to hepatic energy metabolism.

From the finding that the KBR was maintained at high levels by arterialization, the blood flow of which was significantly less than the preclamping THBF, we tried to assess the minimum arterialized blood flow needed to maintain the KBR at high levels. In experiment 2, a significant difference between the levels of KBR at the preclamping THBF and at 8% arterialized blood flow ($P < 0.01$) was observed. The KBR at 12% arterialized blood flow was 0.95 ± 0.09, which was almost the same as the value at the preclamping THBF. These data suggest that the critical point of arterialized blood flow for maintaining the KBR at high levels falls in the range of 8%–12% of THBF. Therefore, it is concluded that the blood flow during arterialization that is essential in order to preserve the viability of the liver is about 10% of THBF. It is thought that the significantly high levels of arterialized portal blood PO_2 contributed to the maintenance of the KBR at high levels despite the low blood flow. On the other hand, a high blood flow may not be necessary for the maintenance of liver viability.

The disadvantage of the arterialization method is that it may cause damage to the liver, although the recent report on the successful long-term clinical use of the method by Pichlmayr et al. is encouraging [18]. One form of damage is due to hemodynamic changes. It has been reported that the hepatic function and architecture are preserved when portal vein flow and pressure are kept within preoperative values [1, 7, 10, 11, 12, 16, 24]. Sheil et al. reported that a satisfactory result was obtained by regulating the arterial shunt flow to less than 1000 ml per minute [19]. Mimura et al. described the controlling of the flow rate from 500 to 600 ml per minute by a motor-driven pump [13]. Another form of damage is that caused to the liver by superoxides produced when ischemic tissue is exposed to high concentrations of oxygen in arterial blood. However, no evidence has been reported to support this theory, at least not for the short period of time involved [24].

In our present data, from the aspect of hepatic energy metabolism, it was demonstrated that the temporary arterialization of the portal vein is an advantageous method for minimizing or avoiding ischemic damage to the liver, and that the minimum arterial blood flow for maintaining liver viability is only about 10% of THBF.

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