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Lactate Generation by Liver in Hemorrhagic Shock[1] (41264)

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Abstract. Hemorrhagic shock caused a decreased hepatic vein PO_2 and pH. This anoxia and acidosis was associated with an increased hepatic vein lactate greater than the arterial and portal vein lactate. This is a reversal of the normal state in which the liver is a consumer of lactate. The normal lactate relationship readily returned following reinfusion of the blood if the hepatic vein PO_2 and pH also returned to normal. However, following a subsequent hemorrhage and reinfusion, the liver continued to produce lactate and the hepatic vein pH remained acidotic, even though the hepatic vein PO_2 returned to the control level. Previous studies had shown that catheterization of the hepatic veins in the dog traumatized the liver and the blood samples from that catheter may be misrepresentative of the true state of hepatic venous blood. A study of the level of lactate, PO_2, pH, PCO_2, and indocyanine green (ICG) compared blood specimens obtained from individually cannulated hepatic veins to those from a "common hepatic venous channel" (CHVC). Hepatic blood samples from the two sites showed no differences for lactate, pH, PCO_2, and ICG in the range studied. The CHVC was more dependable for obtaining specimens during profound shock and gave more valid PO_2 levels for the lower oxygen tensions below 15 mm Hg.

Under normal conditions, lactate generated by peripheral tissue is used for gluconeogenesis in the liver. Oxygen deprivation from multiple mechanisms increases peripheral tissue lactate production, and, if severe enough, the liver will even produce lactate. Schröder *et al.* (1) demonstrated liver lactate production with reduced oxygen consumption during experimental low liver blood flow in dogs. A hepatic vein PO_2 of 24 mm Hg seemed to be the level of anoxia at which the liver became a producer of lactate rather than a consumer (2). Adverse influences other than anoxia can also cause a production of lactate by the liver. Ethanol (3) and alkalosis, as well as reduced liver blood flow from Trimethaphan and hemorrhage (4), cause a higher lactate concentration in the hepatic vein than in the hepatic artery.

In addition, severe acidosis has been shown to cause decreased consumption of lactate in primary hepatocyte culture (5) and production of lactate in isolated perfused livers (6). The present studies were undertaken to determine if lactate production by canine liver was a consistent finding in hemorrhagic shock and to determine the levels of hepatic venous anoxia and acidosis temporally related to the production of lactate.

During these studies, the question of artificially high hepatic vein lactate due to direct cannulation of the vein was considered. Some authors believe introduction of a catheter into a hepatic vein is traumatic, at least in the dog, since obstruction of the vein may cause reflux and stagnation of blood in the hepatic parenchyma due to the low differential pressure between the liver sinusoids and hepatic vein (7). A "common hepatic venous channel" (CHVC) created by occlusion of the posterior vena cava (PVC) above the level of the renal and adrenal veins, with sampling of the blood pooled in the pouch above the obstruction, has been recommended as an alternate sampling technique for hepatic blood. Studies comparing blood lactate levels from CHVC and hepatic vein catheterization

[1] In conducting the research described in this report, the investigators complied with the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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have shown some differences (8). We have extended these comparisons to include the range of lactate and blood gas concentrations seen in hemorrhagic shock.

Methods. Twelve mongrel dogs, fasted for 16 hr, weighing 9 to 18 kg, were anesthetized with Pentothal Na, 20 mg/kg, iv. Supplements of anesthetic were given during preparation and catheterization of the animals. No additional anesthetic was necessary after shock was induced (*vide infra*). An endotracheal tube was inserted, but no mechanical ventilation or oxygen was given. In all dogs, a radiopaque catheter, 5 fr, was placed into a hepatic vein under fluoroscopic visualization by way of either the femoral or jugular veins. The position of the catheter was reconfirmed at the completion of the study by autopsy or fluoroscopy. During the study, the catheter was occasionally wedged into the liver for a few seconds by progressing it 2–3 cm, but no specimens were taken in this position. This gave assurance that the catheter was in position, since the catheter may dislodge from the hepatic vein. Samples were taken when the catheter was maintained in a position that allowed free flow of contrast material around it with no "staining" of hepatic radical following the injection of contrast solution into the catheter.

In order to evaluate the influence of hepatic vein catheterization on the levels of lactate pH, PCO_2, PO_2, and ICG, comparison was made of blood specimens from individually sampled hepatic veins to the CHVC as described (8). Samples were taken within 120 sec of one another by both avenues during control and shock periods. Whole-blood lactate was determined in duplicate (Calbiochem Rapid Lactate Kit). Blood gases were determined on a Radiometer. Blood was drawn into a 10-ml glass syringe previously rinsed with heparin (1000 u/ml), kept in ice water, and assayed within 20 min. Two milligrams of ICG was injected iv as a single bolus and determined on heparinized plasma at 805 nm, and is reported as OD units (HW&D Brand: Cardio-Green). Statistical analysis was by linear regression, employing the General Program Library Listings and Wang 2200 computer.

In six dogs, a CHVC was created by advancing an Edwards Laboratory 5-fr balloon catheter, with sampling port in the tip, through the femoral vein and up the PVC to a level just cephalad to the kidneys. The balloon was inflated, obstructing the blood flow in the PVC from the renal veins and below. CHVC blood was sampled through the port at the tip of the catheter. The correct position of the catheter at a level in the PVC above the renal veins was determined radiographically at the time of direct cannulation of the hepatic vein. Radiopaque dye (Renographin) injected into the femoral vein demonstrated that no dye passed the inflated balloon while the dye filled the PVC and the renal veins. The kidneys were also visualized on X ray of the abdomen or by an intravenous pyelogram. Direct palpation of the inflated balloon with regard to the renal veins and adrenal veins confirmed the position at laparotomy.

In these six dogs, PE 50 polyethylene tubing was placed into the portal vein for blood sampling. A 7-fr catheter was placed in the femoral artery for the recording of blood pressure and hemorrhage. One to two hours were required for preparation of the dog for the experiment. Samples were obtained from all ports in each dog at the indicated times. The samples of femoral artery blood were taken as equivalent to hepatic artery blood.

The blood volume was estimated to be 7% of the body weight. Forty percent of the blood volume was removed from the arterial line at a rate of 50 ml/min using a De Bakey pump, and was pooled in 125 ml of saline with 1000 units of heparin. The blood was maintained at 37° with continuous bubble aeration. The blood pressure was maintained at a systolic pressure of 40 mm Hg by either additional exsanguination or infusion of hemorrhaged blood. After 30 min, the animal's blood was returned at the rate of 50 ml/min into the PVC. The infused blood was sampled for lactate and blood gas determination at the time of reinfusion.

The dogs were subjected to a second identical exsanguination and reinfusion 90 min after the start of the initial bleeding. The blood pressure was again maintained at 40 mm Hg. Statistically significant differ-

TABLE I. COMPARISON OF BLOOD LEVELS OBTAINED FROM HEPATIC VEIN CATHETERIZATION TO A COMMON HEPATIC VENOUS CHANNEL

	Range	Number[a]	Slope	Y intercept	R^b
Lactate[c]	0.2–9.9	(17)	1.00	0.08	0.983
pH	6.88–7.35	(23)	0.755		0.903
PO_2[d]	15–60	(22)	0.915	3.82	0.885
PCO_2[d]	26.9–96.5	(23)	0.978	0.52	0.945
ICG[e]	0.02–0.521	(17)	1.05	0.04	0.977

[a] Number of paired samples taken within 120 sec.
[b] There was no statistical difference except for the PO_2 below 15 mm Hg.
[c] meq/liter.
[d] mm Hg.
[e] OD units/ml.

ences between specimens at each time interval from the artery and portal and hepatic veins were determined by the Wilcoxan's signed rank test. A hepatic vein lactate exceeding both the artery and portal vein levels was taken as hepatic production of lactate.

Results. Blood samples from an individual hepatic vein cannulated with a 5-fr catheter were compared to the CHVC samples throughout the range of pH, PO_2, PCO_2, ICG, and lactate concentrations. No statistical difference was found (Table 1). The correlation was particularly strong between the two techniques for lactate and ICG. The PO_2 showed an absence of correlation if the level in the CHVC was below 15 mm Hg. We believe this was caused by our inability to obtain air-free hepatic vein catheter samples during profound shock. The comparison for PO_2 below 15 mm Hg was considered invalid, and therefore was not included in the analysis.

The arterial PO_2 after both hemorrhages and infusions was stable (Fig. 1). Hepatic vein PO_2 decreased with both hemorrhages, but recovered to control level following the first infusion and exceeded the control following the second. No statistical difference was found between the portal and hepatic vein PO_2 (9).

All dogs survived the first exsanguination and reinfusion. Three dogs died during the second reinfusion; three dogs survived the completion of the reinfusion, but died within 30 min (the post-transfusion observation period); and six dogs died after the 30-min postreinfusion observation period.

Arterial acidosis developing after the second bleed failed to correct following

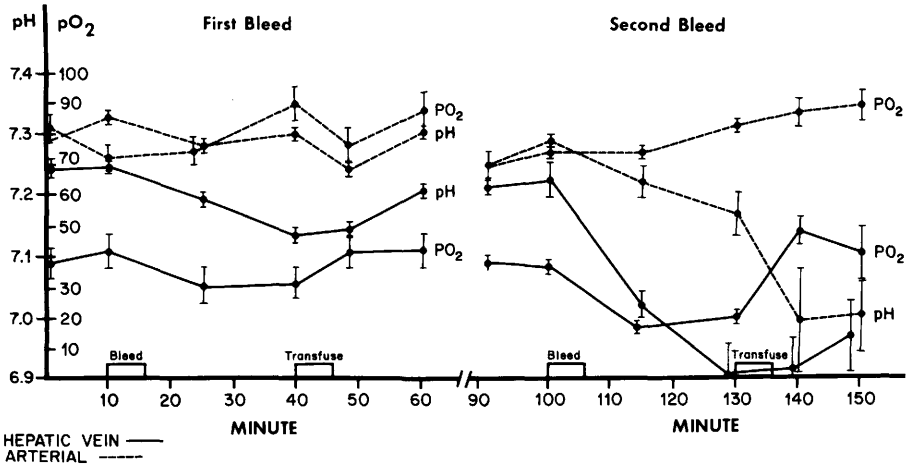

FIG. 1. pH and PO_2 in hemorrhagic shock. Effects of sequential bleeding and transfusion on arterial and hepatic vein pH and PO_2. Bars represent standard deviation about the mean.

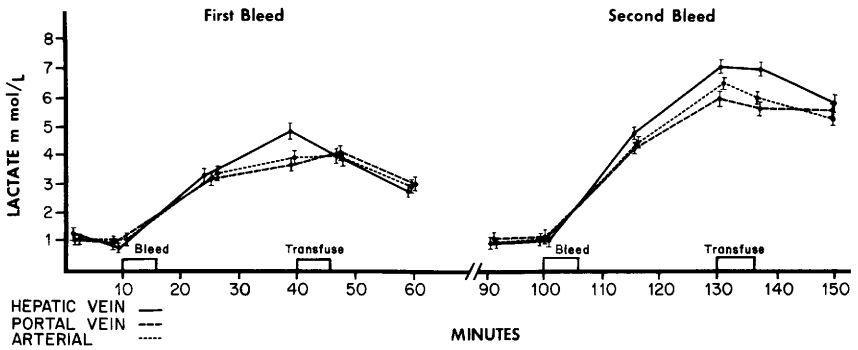

FIG. 2. Lactate in hemorrhagic shock. Effect of sequential bleeding and transfusion on arterial, portal vein, and hepatic vein lactate. The concentration of lactate is significantly higher in the hepatic vein blood than in the arterial and portal vein blood after the first and second bleed and after the second transfusion. Bars represent standard deviation about the mean.

reinfusion despite the small but statistically significant decrease in the arterial lactate (Fig. 2). The hepatic vein pH, however, decreased with both the first and second bleeding. The first reinfusion promptly corrected the hepatic vein pH toward normal, while the second had little effect.

Before hemorrhage, there was no statistical difference in the lactate concentration in the arterial, portal, or hepatic vein blood samples. The initial bleeding caused an increase in hepatic venous lactate greater than the increase in arterial or portal lactate in every dog, $P < 0.05$ (Fig. 2). Reinfusion caused a decrease in hepatic vein lactate significantly more rapid than the arterial decrease.

Following the second hemorrhage, however, the hepatic vein lactate continued to exceed the arterial during the period of observation in every dog despite blood reinfusion. The portal vein lactate was not statistically different from arterial lactate at any time during the experiments. The reinfused blood had an elevated PO_2, reduced PCO_2, and was alkalotic as would be expected. The lactate levels of the reinfused blood, however, were unchanged from control, perhaps because of the dilution with heparinized saline.

Discussion. The possibility of sampling error from hepatic vein cannulation was first raised by Sapirstein and Reininger (7). Using 7- and 8-fr cardiac catheters "inserted as far as possible . . . and withdrawn slightly (1–2 cm)," they compared the blood concentration of rose bengal in samples obtained at various distances from the orifice of individual hepatic veins to a CHVC sample. They concluded that stagnation and ischemia in the cannulated hepatic vein may have caused low estimations of hepatic blood flow using Fick clearance.

Goldstein *et al.* (8) showed small differences in lactate levels taken from hepatic vein cannulas and CHVC. During the insertion of the catheter, they injected radiopaque dye and stained the hepatic tissue, demonstrating blockage of the vein. They did withdraw the catheter 1–2 cm before sampling, but did not note the size of the catheter used. Using a 9-fr catheter in the hepatic vein, Berry and Scheuer (4) reported no systematically high lactate levels. However, some of their studies used a continuous sampling pump which may have decompressed the vein, although the rate was only 0.2 ml/min. Baker and Shields (10) used a 5-fr catheter for permanent placement into a hepatic vein over a 5-month period with satisfactory results.

The present study used an adaptation of the CHVC. A balloon catheter with a distal sampling port was passed up the PVC. Inflation of the balloon effectively obstructed the PVC, and samples were obtained. The question of the physiological insult of obstructing the vena cava for 20 sec has not been studied. The blood pressure and pulse were the only continuous monitors followed during these studies. They showed no change with inflation of the balloon for

20 sec. A brief hypertensive overshoot could occasionally be identified when the balloon was deflated. Perhaps a mechanism similar to a Valsalva maneuver was taking place. The CHVC is the more rapid and convenient source of uncontaminated pooled hepatic venous blood.

The correlation of determinations was good between the two sampling methods except that during profound shock the hepatic vein catheter PO_2 was higher than the CHVC (Table 1). We believe this was due to the practical problems of drawing blood from the small-bore 5-fr catheter in low perfusion states, since air was often aspirated despite precautions. Even a small bubble of air would have raised the PO_2 when the oxygen tension was low. The lowest CHVC reading was 3.5 mm Hg, while the direct hepatic vein was never lower than 12 mm Hg. Since the differences in the lowest PO_2 range was beyond statistical error, and since the analytical errors would trend toward higher PO_2, only CHVC was used for oxygen tension below 15 mm Hg. Above this level, data from the two sampling ports were interchangeable (Table 1). The correlation between the two nonvolatile substances, lactate and ICG, was excellent.

A critical hepatic vein oxygen tension of 25–30 mm Hg is related to production of lactate by the liver (2). This correlates with data from shock patients who have a dismal prognosis if the oxygen tension in the central venous blood falls below 20 to 30 mm Hg (11).

Our data agree with the concept of hepatic vein anoxia as a cause of hepatic lactate production. Following both bleeds, as the hepatic vein PO_2 decreased, the liver produced lactate. However, while the first reinfusion restored lactate metabolism and PO_2 to normal, the second reinfusion only restored the hepatic PO_2; and lactate continued to be produced by the liver during the limited observation time of this experiment.

The continued production of lactate following the second reinfusion at time intervals of 140 and 150 min despite an increased hepatic vein PO_2 may be related to a persistently low hepatic vein pH. In perfused liver, low pH has been shown to inhibit lactate metabolism (12). Work in our laboratory with hepatocytes in culture has shown that anoxia or low pH independently inhibits lactate metabolism. These effects are readily reversible upon returning to normal atmosphere or pH (5). These *in vitro* data support the concept of acidosis as an inhibitor of lactate metabolism independent of anoxia and humoral mediators of shock.

In the present study, while the initial lactic acidosis may have been caused by the hepatic vein anoxia, the continued hepatic production of lactate after the second reinfusion was temporally related to the persistently low pH and not to a low hepatic vein PO_2, suggesting that whatever the mechanism, the acidosis was self-sustaining at least in the shocked liver (13). This is probably not so with the healthy liver.

Although the *in vitro* studies suggest acidosis as an independent primary cause of inhibited gluconeogenesis from lactate, the present data show only a temporal correlation of hepatic lactate production and hepatic vein acidosis despite normal oxygenation of the hepatic vein blood. Both these abnormalities may be related to a more profound pathophysiologic insult. Since removal of lactate by the liver is an alkalinizing process, it is not surprising that continued lactate production by the liver would be associated with persisting acidosis.

Since the arterial lactate did decrease after the second reinfusion despite the continued output of lactate by the liver, some tissues, among them the kidneys and muscle, must consume lactate in the face of acidosis (14, 15).

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