Portal-Systemic Venous Shunts in Hemorrhagic Shock in the Dog and Monkey

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PREVIOUS studies in this laboratory [1] and by others [4-12] have shown that the monkey does not develop the congestion, hemorrhage, and necrosis of the bowel seen in the dog following hemorrhagic shock. Since the monkey also has less portal pressure elevation following reinfusion of the shed blood, it was postulated that there may be effective portal-systemic venous shunts. Indeed, Child [3] showed that such shunts exist and became active when the primate portal vein is occluded.

To evaluate the presence or absence of shunts and their significance both dogs and monkeys were subjected to a standardized shock procedure. Shunts were detected by injection of an indicator, either ascorbic acid [5] or krypton[85], into the portal vein. Depending upon the indicator, appearance time was then monitored at either the right atrium or in the expired air. This time should be shorter if the indicator passes through a relatively large portal-systemic shunt rather than through the hepatic parenchyma. Prior to the shock studies the sensitivity of the method in relation to the size of the shunt was evaluated.

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Method

To evaluate the sensitivity of the method for detecting shunts with krypton[85], in two dogs an 8 mm. Dacron tube was sutured between the portal vein and the inferior vena cava. A 6 mm. ID electromagnetic flow-through probe was interposed in the shunt. Shunt flow was varied by partially occluding the Dacron tube. The technic for shunt detection with krypton [85] was that described by Long *et al.*[11] Krypton [85] in a concentration of approximately 1.0 mc./ml. was injected into the portal vein and monitored in the expired air of the dog through an endotracheal tube. The animal was ventilated with a piston respirator at 22 breaths/min.

Hemorrhagic shock studies were performed on six dogs and seven monkeys (three *Macacus rhesus* and four *Macacus nemistrina*). The dogs weighed between 11.3 and 16.0 Kg. The rhesus monkeys varied between 11.0 and 14.1 Kg. while the nemistrina or squirrel-tail monkeys ranged from 3.1 to 4.1 Kg. The dogs were given 3 mg./Kg. morphine sulfate intramuscularly and 30 minutes later were anesthetized with 15 mg./Kg. intravenous pentobarbital. The monkeys were initially given 1 mg./Kg. morphine sulfate intramuscularly and 30 minutes later were anesthetized with 12 mg./Kg. methohexital sodium (Brevital-Lilly) given intramuscularly while the animal was held in a squeeze cage. An additional 8–10 mg./Kg. pentobarbital was

given intramuscularly after the animal was taken out of the cage.

Both dogs and monkeys had a cuffed endotracheal tube inserted and were ventilated with air with a piston respirator. The operative procedure in both groups of animals was identical. Under sterile conditions the abdomen was entered and a polyethylene catheter was inserted into a small tributary of the superior mesenteric vein. The catheter was advanced so that the tip was just proximal to the confluence of the mesenteric veins into the portal vein. A ligature was placed loosely around the portal vein just proximal to its entrance into the liver. The abdomen was closed. Polyethylene catheters were inserted into the aorta and inferior vena cava through the femoral vessels. Under fluoroscopic control a platinum electrode was placed via the femoral vein into the middle of the right atrium. The aortic catheter was attached both to a bottle for collection of blood and to an arterial pressure gage. Rectal temperature was monitored and body temperature kept reasonably constant with a heat lamp.

The procedure consisted of a 30-minute control period followed by heparinization (3 mg./Kg.) and hemorrhage to an arterial pressure of 40 mm. Hg. Pressure was maintained at this level by adjusting the height of the bottle attached to the arterial catheter. When 30% of the maximum volume bled had spontaneously been taken back by the animal, the remaining shed blood was rapidly reinfused intravenously and the animal followed until death.

Ascorbic acid was also used as an indicator to assess appearance time at the right atrium, thereby preventing an apparent prolongation of the appearance time noted with krypton^{85} due to delay in the pulmonary circulation or other factors unrelated to changes in mesenteric flow. The appearance time of ascorbic acid was detected by a platinum electrode in the right atrium using a simple potentiometric circuit. Injections of krypton^{85} and ascorbic acid were made at 10 minute intervals throughout the study until death. Krypton^{85} solution was made up in a concentration of approximately 1 to 2 mg./ml. using as diluent a solution of ascorbic acid (40 mg./ml. in physiologic saline). The krypton-ascorbic acid solution was injected into the mesenteric vein catheter and each indicator monitored separately in the right atrium and in the expired air.

In order to verify the presence of shunts the portal vein was intermittently occluded with a ligature at the liver hilus. If the indicator injected into the portal vein proximal to the ligature could still be detected rapidly this would strongly suggest the presence of shunts. The size of the shunt in monkeys was estimated by comparing the area of the ascorbic acid curve before and with portal vein occlusion, assuming adequate mixing of the indicator on injection into the portal vein. In view of previous studies relating the forward triangle to the total area in indicator dilution curves,[6] a comparison of the first portion of the shunt curve and the portal flow curve was made in the monkeys. The area of the forward triangle was obtained by planimetering the area of the curve from the appearance to the peak concentration of the curve.

In order to demonstrate the shunts radiographically, an injection of 60% sodium and methyl glucamine ditrizoate (5 ml.) (Renovist-Squibb) was made into the portal vein of a *Macacus nemistrina*. Cineangiograms were made on 16 mm. film. A similar injection was then made after the portal vein was occluded.

Results

Appearance Time vs. Shunt Flow. Figure 1 shows the changes in krypton^{85} appearance time and cardiac output in an experiment in which an artificial portacaval shunt was opened and closed. It is evident that appearance time was significantly shorter with open shunts. Shunt flows as

small as 5 ml./min. could still be detected. The findings in both dogs were similar.

Hemorrhagic Shock. The duration of hemorrhage averaged 263 min. in the dog (range 158–397) and 164 min. in the monkey (range 55–180). The mean survival time following reinfusion was 217 min. in the dog (range 68–515) and 207 min. in the monkey (range 95–365). All animals died. Average maximum bleeding volume in the dogs was 6.4% of body weight while in the monkey it was only 1.7% of body weight. Figure 2 shows the changes in mean arterial blood pressure (MABP), portal venous pressure (PVP), bleeding volume and krypton^{85} appearance time for both groups of animals during the period of hemorrhage and the period following reinfusion.

Following hemorrhage, when arterial pressure was set at 40 mm. Hg, portal venous pressure initially fell but then returned to near control levels in both dog and monkey. With reinfusion of the shed blood, both dog and monkey had a rise in arterial pressure, although this remained 17 and 12 mm. Hg below control levels in each group of animals, respectively. In both groups there was then a gradual decline until death. Portal venous pressure rose above normal in both dog and monkey but to much less an extent in the latter. In general, it then followed the pattern of the arterial pressure until death.

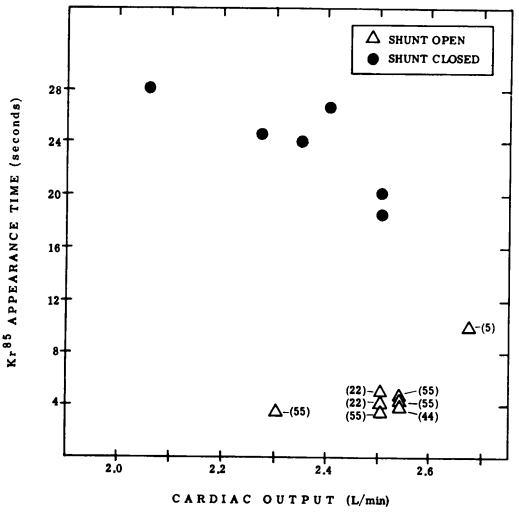

FIG. 1. Relationship of krypton^{85} appearance time and the size of a surgical shunt in a dog. Figures in parentheses are shunt flows in ml./min.

Krypton^{85} appearance time in the dog, after a brief initial fall, tended to rise in the oligemic phase. The changes in the monkey differed from those in the dog in that after hemorrhage krypton^{85} appearance times were more prolonged, although both groups of animals exhibited wide standard errors. Following reinfusion, krypton^{85} appearance times showed a marked shortening in both dog and monkey, falling significantly below the control values. In the dog the mean krypton^{85} appearance time was 51% of control while in the monkey it was 62% of control. In both groups of animals the time gradually lengthened and after 60 to 80% of postinfusion time it was longer than control values.

Comparison of Indicators. Figure 3 shows a comparison of the appearance time of krypton^{85} and ascorbic acid. As would be expected from the location of the detecting devices, the appearance time of ascorbic acid was always shorter than that of krypton^{85}. However, the two appearance times did not always have the same relationship to each other. During both the period of hemorrhage and following reinfusion krypton^{85} was proportionately slower in appearance than ascorbic acid.

Portal Vein Occlusion. To validate the conclusion that a shortened appearance time of the indicator in the postinfusion period signified a shunt between the portal and systemic veins, the portal vein was occluded close to the liver hilus. In all but two dogs krypton^{85} could not then be detected in the expired air, indicating the absence of significant shunts. In two dogs the appearance time was much longer than without occlusion, suggesting a shunt with a long circuitous route. When the portal vein in the monkey was occluded the appearance time of krypton^{85} and ascorbic acid became markedly shortened when

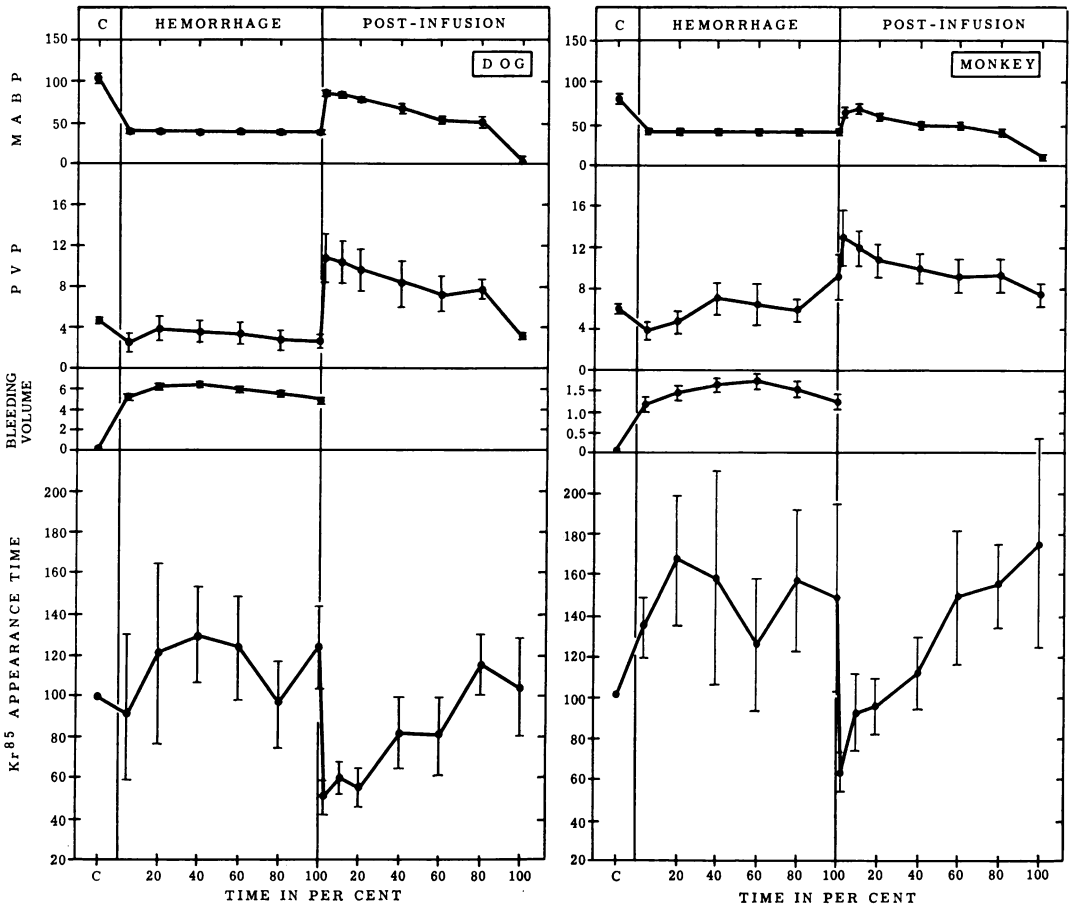

FIG. 2. Mean and standard errors for 6 dogs (left) and 7 monkeys (right) during hemorrhagic shock and reinfusion. C, control period; MABP, mean arterial blood pressure (mm. Hg); PVP, portal venous pressure; bleeding volume in per cent of body weight; krypton^{85} appearance time as per cent of control; time in per cent of period, reinfused at 100% of hemorrhage period.

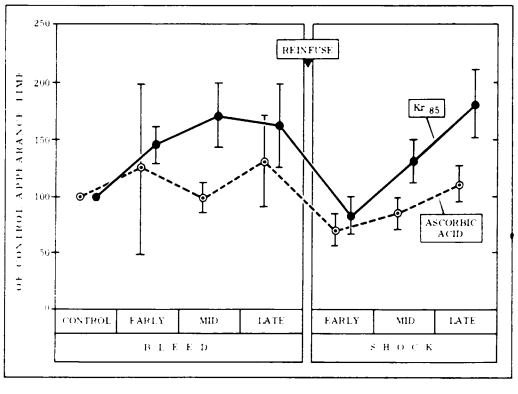

FIG. 3. Relationship of krypton^{85} appearance time and ascorbic acid appearance time as per cent of control during the period of hemorrhage and following reinfusion. Mean and standard errors are shown for 5 monkeys.

compared to control times (Fig. 4). In both groups of animals the portal pressure rose with occlusions but this was less in the monkey (mean ± SE: 29.2 ± 1.8 mm. Hg) than in the dog (36.0 ± 1.9 mm. Hg).

The area of the forward triangle was obtained in 6 pairs of ascorbic acid curves in the monkeys before and after portal vein occlusion. The shunt curve forward triangle (portal vein occluded) had a mean area of 80.2% (range 63.6 to 100.0%) of the portal flow curve forward triangle (portal vein patent), thus indicating a moderately large shunt.

Cineangiogram. The cineangiogram with a patent portal vein showed that the con-

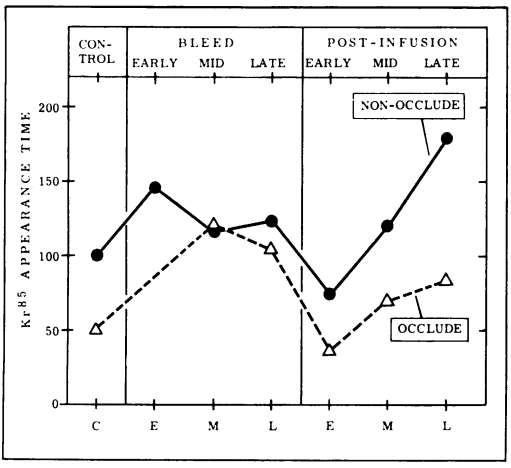

FIG. 4. Comparison of krypton^{85} appearance time with and without portal vein occlusion in 4 monkeys during hemorrhage and following reinfusion. C, control period. Bleeding and post-infusion periods are divided into early (E), middle (M), and late (L) portions.

trast material readily passed through the liver into the thoracic inferior vena cava and right atrium. Little opaque media was seen in the portal vein tributaries. With occlusion of the portal vein many portal vein tributaries were apparent but no contrast material was seen in the liver and portal vein segment distal to the ligature (Fig. 5A, B). A long venous channel, possibly the inferior mesenteric vein, could be seen passing down into the pelvis and contrast material was evident in the thoracic inferior vena cava and right atrium.

Discussion

The use of krypton^{85} in the detection of portal systemic venous shunts was first described by Long, Lombardo, and Braunwald.[11] They showed that the major factor

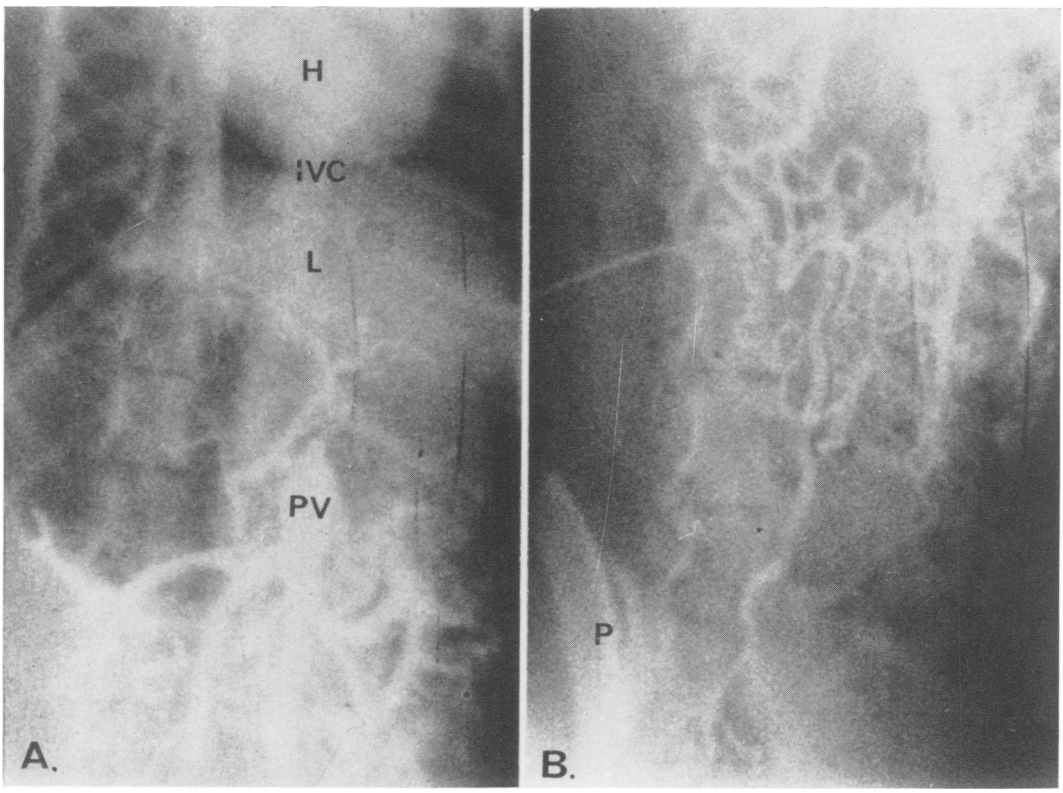

FIG. 5. Cineangiogram after injection of radio-opaque media into the portal vein of a monkey. The portal vein is occluded just proximal to liver hilus. A) Views showing little media beyond the occluded portal vein. However, the inferior vena cava is well outlined by the contrast material. H, heart; IVC, inferior vena cava; L, liver; PV, portal vein. B) Views showing portal vein tributaries including a tortuous vessel passing down into the pelvis (P).

affecting appearance time of radioactive gas in the expired air, as monitored with a Geiger-Mueller tube, was whether the gas traversed the liver capillary bed or was shunted directly from portal vein to the vena cava. It is apparent that the rate of diffusion of the krypton^{85} gas across the pulmonary alveolar membrane would significantly affect appearance time. Indeed, the differences between the changes in appearance time of ascorbic acid and krypton^{85} in our study were initially thought to be due to a decreased rate of diffusion associated with hemorrhagic shock. However, studies in this laboratory and by others [7] have shown that there is little change in pulmonary diffusion in the dog when studied with carbon monoxide absorption in the post-infusion phase of hemorrhagic shock. We cannot at present explain this proportionately longer appearance time of the krypton^{85} when compared to ascorbic acid. A slower circulation in the lung capillaries with increased dilatation may be the cause.

In view of the studies with measured portal systemic shunts the method appears quite sensitive for detecting shunts as small as 5 ml./min. An estimation of the size of the shunt in the monkeys can be made by comparing the area of the ascorbic acid curve before and with complete portal vein occlusion, provided there is adequate mixing of the indicator when injected into the portal vein. If the area of the curve, obtained when the portal vein is patent, correlates inversely with the portal vein flow, then the curve during portal vein occlusion should give the relative size of the shunt as compared to the portal flow. The area of the forward triangle was substituted for the total area of the curve since the second portion of the curve was often difficult to outline due to a slow return to the baseline. In 6 pairs of ascorbic acid curves from three monkeys the shunt curve forward triangle (portal vein occluded) had a mean of 80.2% of the portal flow curve forward triangle (portal vein patent). This would suggest that these shunts are quite large.

Although both dogs and monkeys showed a significantly shortened appearance time on reinfusion, portal vein occlusions followed by injection of krypton^{85} behind the obstruction failed to show any significant shunt in the dog, while in the monkey the indicator was rapidly detected, thereby suggesting a shunt. The shortened appearance time in the dog must be due to other factors than portal systemic shunting. Intrahepatic venous constriction and closure of the postsinusoidal sphincters are known to occur in shock in the dog and are responsible at least in part for the increased portal pressure and reduced blood flow through the liver with resulting stasis.[9, 13] Stasis in a sufficiently large number of channels would force the blood, under high pressure in the portal vein, through the reduced number of open channels at a greater velocity than normal, thus leading to a shortened appearance time of the indicator.

The presence of anatomic connections between the portal vein and inferior vena cava has been known for many years and was summarized recently by Knisely and Comer.[8] The present study shows that these venous connections function in monkeys but not in dogs. The significance of these shunts is not altogether clear. From Child's studies,[3] it is evident that the shunts protect the monkey from fatal splanchnic pooling when the portal vein is ligated. Nevertheless, in our studies portal pressure did rise with occlusion, although to a lesser extent than seen in the dog. Although our previous studies [1] and those of others [12] did not show a portal pressure overshoot on reinfusion in the monkey, that was not true in this study, where the monkeys showed elevation of portal pressure greater than control values with reinfusion. This rise was less significant than in the dog and may have been due to the re-

peated injections into and manipulation of the portal vein resulting in some venous constriction. In addition, the dog showed the typical bowel lesion while the monkey intestine again failed to show any hemorrhagic necrosis.

Others have shown that dogs with surgical portacaval shunts are not protected from the characteristic lesion.[10] Bounous and his associates[2] demonstrated that the canine lesion at least in part is due to proteolytic enzymes of the pancreas acting on intestinal mucosa which has been damaged by ischemia. Gurd (personal communication) suggested that the monkey, a vegetarian in contrast to the dog, may secrete less enzymes and therefore have less autodigestion of the intestine with shock. Perhaps a combination of these factors along with portal decompression by portal-sytemic venous shunts may account for the different picture of hemorrhagic shock in the monkey as compared with the dog.

Summary

Irreversible shock is accompanied by gross congestion in the small bowel of the dog but not of the primate. To investigate the possible role of portal-systemic shunts as alternate pathways to drain the splanchnic circulation in the monkey, krypton^{85} and ascorbic acid were injected into the portal vein. The isotope was monitored by a Geiger-Mueller tube in the expired air; ascorbic acid was detected by a platinum electrode in the right atrium. Appearance times were sensitive to artificial portal-systemic shunt flows of 5 ml./min. Six dogs and seven macaque monkeys anesthetized with morphine sulfate and nembutal were subjected to a standardized hemorrhagic shock procedure. In the dog and the monkey appearance time was shortened by $51.0 \pm 8.6\%$ and $62.1 \pm 9.1\%$ of control respectively with reinfusion of the shed blood. When the portal vein was occluded, the appearance time in the dog was either greatly prolonged or the indicator never appeared. In the monkey, with portal vein occlusion, the appearance time became shortened suggesting portal-systemic shunts. Although both dog and monkey had elevation of the portal pressure with occlusion, this was more pronounced in the dog (monkey: 29.2 ± 1.8 mm. Hg; dog: 36.0 ± 1.9 mm. Hg). This study suggests that portal-systemic shunts do decompress the portal vein in the monkey during hemorrhagic shock.

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