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PORTAL HEMODYNAMICS

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Studies of the effects and modes of action of autonomic drugs on portal hemodynamics

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It has been known for many years that certain autonomic drugs cause changes in portal hemodynamics. In 1909, Schmid¹⁸ demonstrated that epinephrine caused a transient rise in portal pressure. In 1928, Clark⁷ and later McMichael¹⁷ and others showed that pitressin caused a temporary fall. These findings were chiefly of physiologic interest until recently. However, in 1956, Kehne and associates¹³ and subsequently Schwartz and his group¹⁹ demonstrated that pitressin was of value for lowering the portal pressure in patients with bleeding esophageal varices. Davis and colleagues⁸ showed the same effect by direct esophagosopic examination and by intrasplenic pulp pressure measurements. Since the publication of these reports, studies by Eiseman¹⁰ and Johnson¹¹ and their associates have focused on the possibility that this effect is due to pharmacologically induced closure of arteriovenous shunts in the gastrointestinal tract. More recently, it has been shown by Cincotti and co-workers⁶ that Arfonad, one of the ganglionic blocking agents, also causes a reduction of portal pressure.

The purpose of the present study was to determine what role the liver itself had in

the portal pressure changes evoked by epinephrine, pitressin, and Arfonad. The results of these experiments tend to verify some accepted beliefs as to the reason why these drugs alter portal pressure. However, they also show that other accepted mechanisms may be incomplete.

METHODS

Fifty-five mongrel dogs which weighed 7 to 18 kilograms were used. For all pressure studies the dogs were anesthetized with 23 to 27 mg. per kilogram of pentobarbital sodium. A citrate-filled polyethylene catheter was placed in a carotid artery and connected to an aneroid manometer for arterial pressure (Fig. 1). A similar catheter was placed in the inferior vena cava via a femoral vein and a smaller catheter passed into the portal vein via one of the mesenteric radicles (Fig. 1). The venous catheters were attached to glass manometers which were leveled with the anterior vertebral bodies of the upper lumbar vertebrae by the method of Taylor and Herbert.²³

In all experiments, only 1 drug was used. The test dose of epinephrine was 0.25 ml. of 1/1000 solution. The test dose of pitressin was 10 U. The pitressin and epinephrine were diluted in 35 ml. saline solution and given into a foreleg vein. The injections were made with a constant infusion pump (Fig. 1) in 5 minutes, after preliminary

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demonstration that similar control injections with saline solution did not affect any of the pressures. Arfonad was diluted with saline solution to 0.1 mg. per milliliter and given intravenously at whatever rate was necessary to obtain the desired hypotensive effect.

Experiments were carried out in normal dogs and in dogs with portacaval transposition. In some instances the operation had been performed from 2 weeks to 2 months prior to testing, and in others the tests were performed approximately 2 hours after completion of operation. The transposition was accomplished by a technique developed in this laboratory.²² The method consisted of portacaval transposition above the level of the adrenal veins and proximal to all the tributaries of the portal vein.

RESULTS

The effect of epinephrine.

Normal dogs. Seven normal dogs were studied. The results were the same in all experiments and conformed to those of previous investigators.^{2, 5, 12, 14} Pressure changes generally lasted less than 10 to 15 minutes. The arterial, vena caval, and portal pressures all rose (Fig. 2, A). In every case the portal rose more than the vena caval pressure. The average rise in portal pressure was 131 mm. citrate, and the rise in vena caval pressure averaged 41 mm. citrate (Fig. 5, A).

Dogs with portacaval transposition. Twelve dogs were studied. The duration of pharmacologic effect was generally less than 10 to 15 minutes. The arterial pressure rose in all cases. Pressures in the inferior vena cava, proximal to the hepatic capillary bed (Fig. 2, B), rose in all 12 dogs. The average increase was 128 mm. citrate. Pressures in the portal vein which now connected directly into the systemic circulation were increased in 11 dogs and decreased in 1. The average change of portal vein pressure for all 12 dogs was a 35 mm. citrate rise (Fig. 5, A).

The effect of pitressin.

Normal dogs. Seven normal dogs were tested. The arterial pressure rose in all,

usually only slightly (Fig. 3, A). The portal pressure declined in all 7 dogs (Fig. 3, A), the average drop being 31 mm. citrate (Fig. 5, B). In 5 of the 7 animals, rises were noted in the vena caval pressure and in the other 2 it remained the same. The average change in the vena caval pressure of the 7 dogs was a 7 mm. saline increase (Fig. 5, B). In most dogs the various pressure changes lasted for 20 to 30 minutes.

Dogs with portacaval transposition. Seven dogs with portacaval transposition were tested. Five of the animals were studied within 2 hours after the operation, and the other 2 were studied 2 months after operation. In all 7 experiments, the arterial pressure rose (Fig. 3, B). The vena caval pressure proximal to the hepatic capillary bed fell in all 7 dogs (Fig. 3, B). The average change in the 7 dogs was an 18.5 mm. citrate decline (Fig. 5, B). In the portal vein, which had been redirected into the proximal vena cava, the pressure fell in 6 of 7 experiments (Fig. 3, B), and was unchanged in the other. The average change for the 7 dogs

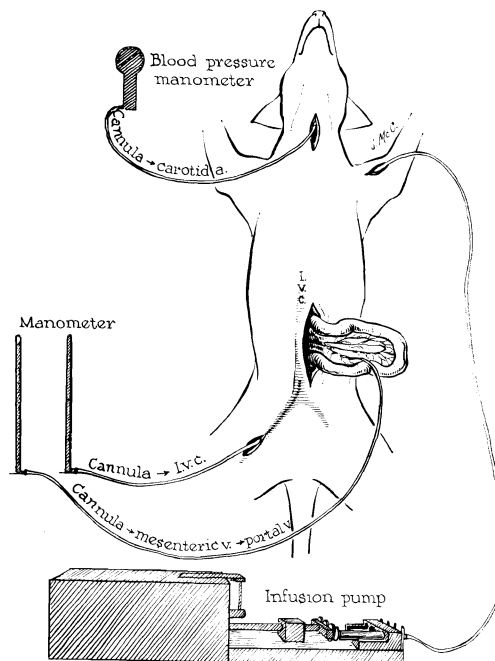


Fig. 1. Experimental setup used for pressure determinations and drug administration.

was a fall in the portal pressure of 35 mm. citrate solution (Fig. 5, B).

The effect of Arfonad.

Normal dogs. The hypotensive response was used as a guide for the administration

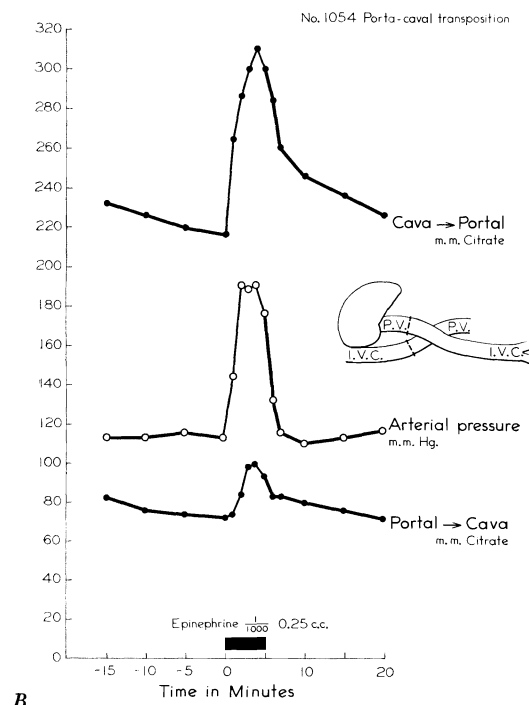
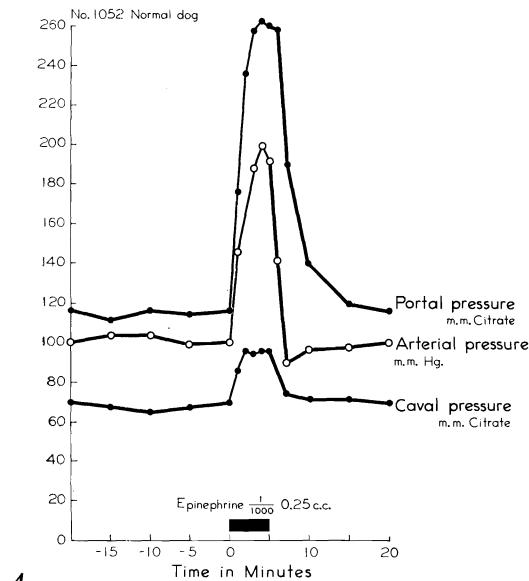


Fig. 2. Effect of epinephrine on vascular pressures in (A) normal dog and (B) dog with portacaval transposition.

of Arfonad. The blood pressure dropped from 15 to 70 mm. Hg during the test period (Fig. 4, A). In 6 of the 7 dogs, the portal pressure declined and in the other it was unchanged. The average portal pressure change was a 22 mm. citrate fall (Fig. 5, C). The vena caval pressure rose slightly in 4 dogs, was unchanged in 1, and fell in the other 2. After cessation of administration of Arfonad, the venous pressures returned to control values concomitantly with the restoration of the arterial pressures (Fig. 4, A).

Dogs with portacaval transposition. Fifteen dogs were tested, 4 immediately after transposition and 11 in 2 weeks or more after operation. The vena caval pressure proximal to the hepatic capillary bed rose in 7 animals (Fig. 4, B), was unchanged in 6, and fell in 2. In the portal vein, which drained into the proximal vena cava, the pressure fell in 11 dogs (Fig. 4, B), was unchanged in 2, and increased in 2. The average change in portal pressure in all 15 dogs was a 22 mm. citrate fall (Fig. 5, C).

DISCUSSION

In the interpretation and application of any study such as the present one, the species difference between the experimental animal and man is always carefully considered. Such a precaution is especially germane when dogs are used for portal pressure studies. The intrahepatic venules and veins have extremely well-developed smooth muscle coats in the dog,¹ and these are thought to provide unusual control of hepatic vascular resistance.^{3, 4, 9, 16, 21, 24} This anatomic feature is absent or poorly represented in man and most other species.¹ Furthermore, the capacity for vasomotor change in the human liver may be further decreased by the presence of cirrhosis, the very situation in which drugs would be used to alter portal pressure.

With this reservation in mind, the present study was designed to determine what role the liver played in the action of various autonomic drugs on portal pressure. Transposition of the vessels deviated the splanchnic

nic drainage directly into the central venous pool and precluded a hepatic factor from influence on portal pressure. Conversely, the vena caval pressure was brought under the influence of changes in resistance of the hepatic vascular bed. The testing procedures used were performed in exactly the same way in every experiment. The constant infusion pump which was used to inject all drugs except Arfonad added a uniformity which has often not been present in other studies of autonomic agents.

With an injection of epinephrine, the rise in portal pressure appeared largely to be related to the necessity for the splanchnic venous blood to pass through the liver. When transposition was performed, rises in portal pressure were small. By contrast, the trans-hepatically directed vena cava now exhibited major increases compared to small pressure rises in the normal animal. Theoretically, these pressure changes could be explained by the assumption that the liver imposed a fixed resistance to venous blood transport, and that epinephrine greatly increased the

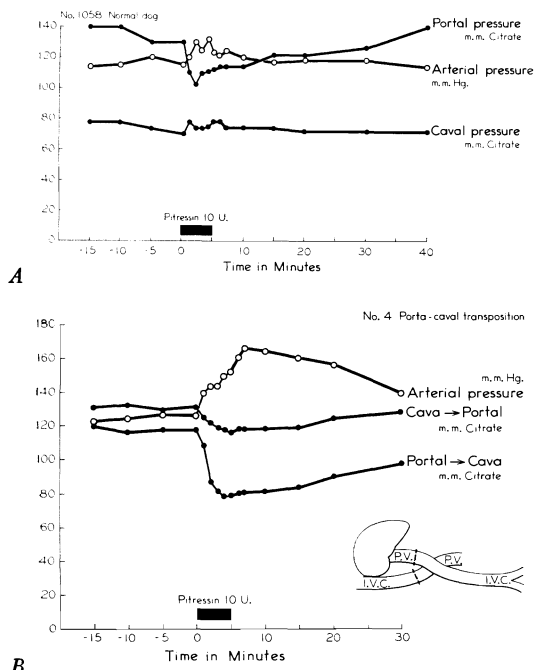


Fig. 3. Effect of pitressin on vascular pressures in (A) normal dog and (B) dog with portacaval transposition.

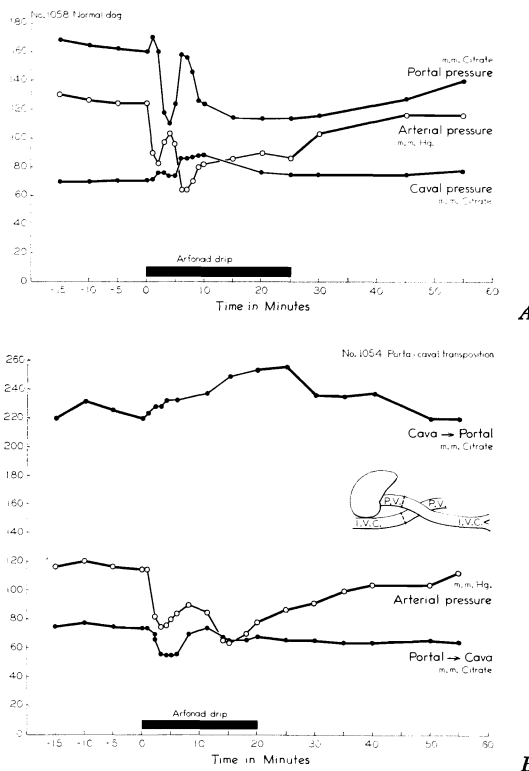


Fig. 4. Effect of Arfonad on vascular pressures in (A) normal dog and (B) dog with portacaval transposition.

venous return in both the portal vein and vena cava. In this way the venous channel passing through the liver would have a disproportionate rise in pressure due solely to an increased flow rate. There is, however, overwhelming evidence^{2-4, 9, 15, 16, 20, 25} that the liver plays more than a passive role after administration of epinephrine, and its vascular bed undergoes active constriction.

Recently, Eiseman¹⁰ and Johnson¹¹ and their associates have presented an explanation for the clinically important fact that intravenous pitressin causes a fall in portal pressure. Their data indicated that pitressin prompted closure of arteriovenous enteric shunts, thereby reducing the volume of portal blood flow. The present experiments support such a concept of peripheral action, inasmuch as substantial reductions in portal pressure were seen after transposition.

The present studies, however, also focus attention on an auxiliary mechanism for

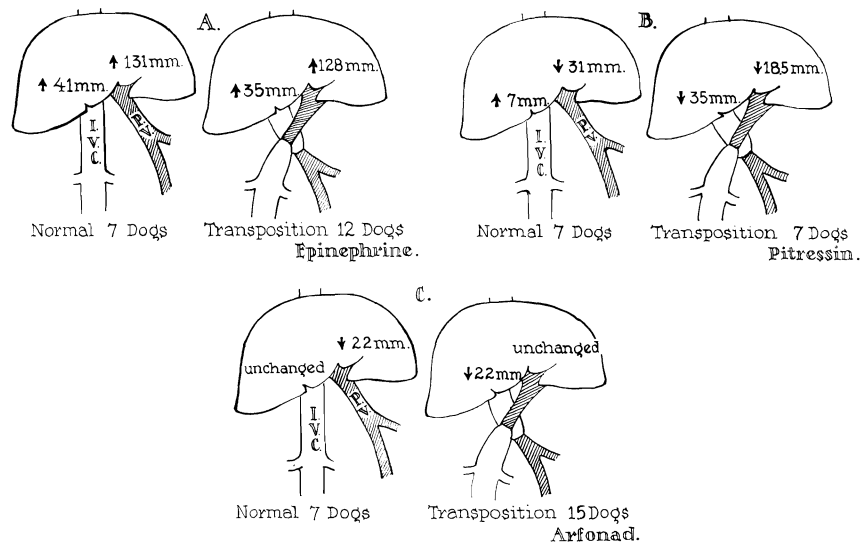


Fig. 5. Average pressure changes with administration of (A) epinephrine, (B) pitressin and (C) Arfonad.

pitressin-induced reduction of portal pressure involving a fall of hepatic vascular resistance. In animals in the normal state, pitressin usually caused a slight rise in vena caval pressure. When the vena caval flow was directed through the liver, pitressin caused a reverse effect with a pressure fall in every case. In the treatment of portal hypertension, this factor is probably of limited significance since the rigid and fibrosed liver has probably lost much of its capacity for direct vascular response.

The present study indicates that Arfonad has no direct action on the hepatic vascular system and that its principal effect is on the peripheral splanchnic bed. A consistent fall in portal pressure was observed whether the splanchnic flow was or was not passing through the liver. Similarly, the pressure behavior of the transposed vena cava was not changed from that seen in normal dogs. Whether the extrahepatic effect of portal pressure reduction with Arfonad is due to a simple reduction in arterial inflow, to closure of arteriovenous shunts, or to some other mechanisms is not clear.

SUMMARY

The effect of epinephrine, pitressin, and Arfonad on portal pressure has been studied

in dogs with special emphasis on the role of the liver in determining pressure changes. The use of dogs with portacaval transposition allowed portal pressures to be studied with the exclusion of any hepatic vascular factor. With this preparation, vena caval pressures were brought under the influence of changes in hepatic vascular resistance.

By this technique, the action of epinephrine in raising portal pressure primarily seemed to be due to an increase in hepatic vascular resistance. The action of pitressin in reducing portal pressure appeared to be due to a combination of reduction of splanchnic blood flow and a reduction in hepatic vascular resistance. The effect of Arfonad in lowering portal pressure appeared to be unrelated to any changes in the liver itself.

REFERENCES

1. Arey, L. B.: Throttling veins in the livers of certain animals, *Anat. Rec.* **81**: 21, 1941.
2. Bainbridge, F., and Trevan, J.: Some actions of adrenalin on the liver, *J. Physiol.* **51**: 461, 1917.
3. Bauer, W., Dale, H. H., Poulsson, L. T., and Richards, D. W.: The control of circulation through the liver, *J. Physiol.* **74**: 343, 1932.
4. Burton-Opitz, R.: The vascularity of the liver. VIII. The influence of adrenalin on

- the arterial inflow, *Quart. J. Exper. Physiol.* 5: 309, 1912.
5. Child, C. G.: *The hepatic circulation and portal hypertension*, Philadelphia, 1954, W. B. Saunders Company.
 6. Cincotti, J., Welch, H., Carter, J., Cleary, J., Boba, A., and Nelson, J.: Reduction of portal hypertension by non-shunting methods in patients with cirrhosis, *S. Forum.* 11: 276, 1960.
 7. Clark, G. A.: A comparison of the effects of adrenalin and pituitrin on the portal circulation, *J. Physiol.* 66: 274, 1928.
 8. Davis, W., Gorlin, R., Reichman, S., and Storaasli, J.: Effect of pituitrin in reducing portal pressures in the human being, *New England J. Med.* 256: 108, 1957.
 9. Deysach, L. J.: The nature and location of the "sphincter mechanism" in the liver as determined by drug action and vascular injections, *Am. J. Physiol.* 132: 713, 1941.
 10. Eiseman, B., Silen, W., Tyler, P., and Earley, T.: The portal hypertensive action of pituitrin, *S. Forum.* 10: 286, 1959.
 11. Johnson, L., Nelson, H., Hardesty, W., and Peskin, G.: Enteric arteriovenous anastomoses and their contribution to portal hemodynamics, *S. Forum.* 11: 272, 1960.
 12. Katz, L., and Rodbard, S.: The integration of the vasomotor response in the liver with those in other systemic vessels, *J. Pharmacol. & Exper. Therap.* 67: 407, 1939.
 13. Kehne, J., Hughes, F., and Gompertz, M.: The use of surgical pituitrin in the control of esophageal varix bleeding, *SURGERY* 39: 917, 1956.
 14. Lamson, P., Abt, A., Oosthuisen, C., and Rosenthal, S.: The influence of the arterial blood supply to the liver on hemoglobin concentration in certain acute conditions, *J. Pharmacol. & Exper. Therap.* 21: 401, 1923.
 15. MacLeod, J., and Pearce, R.: The outflow of blood from the liver as affected by variations in the condition of the portal vein and hepatic artery, *Am. J. Physiol.* 35: 87, 1914.
 16. Maegraith, B. G.: *Microanatomy of the hepatic vascular system*, Tr. Josiah Macy, Jr., Foundation, pp. 181-204, 1951.
 17. McMichael, J.: The portal circulation, *J. Physiol.* 75: 241, 1932.
 18. Schmid, J.: Influence of pressure and volume of the blood stream in the portal vein by breathing and by experimental occlusion, *Pflüger's Arch. ges. Physiol.* 126: 165, 1909.
 19. Schwartz, S., Bales, H., Emerson, G., and Mahoney, E.: The use of intravenous pituitrin in treatment of bleeding esophageal varices, *SURGERY* 45: 72, 1959.
 20. Seneviratne, R. D.: Physiological and pathological responses in the blood vessels of the liver, *Quart. J. Exper. Physiol.* 35: 77, 1949.
 21. Simonds, J. P.: A study in the simultaneous changes in blood pressure in the carotid artery and jugular and portal veins in anaphylactic and peptone shock in dogs, *Am. J. Physiol.* 65: 512, 1923.
 22. Starzl, T. E., Butz, G. W., Jr., and Munger, D. H.: A technique for portal caval transposition, *J. S. Res.* 1: 218, 1961.
 23. Taylor, F., and Herbert, L.: Portal tension, *Surg. Gynec. & Obst.* 92: 64, 1951.
 24. Thomas, W. D., and Essex, H. E.: Observations on the hepatic venous circulation with special reference to the sphincteric mechanism, *Am. J. Physiol.* 158: 302, 1949.
 25. Wakin, W. G.: The effect of certain substances on the intrahepatic circulation of blood on the intact animal, *Am. Heart J.* 27: 289, 1944.