The Role of the Liver in the Adrenergic Regulation of Blood Flow from the Splanchnic to the Central Circulation

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Cardiac output is determined, in large part, by the venous return of blood to the heart. Various adrenergic and pharmacologic influences affect venous return. In the dog it appears that the liver may play an important role in the control of blood flow from the splanchnic to the central circulation and, hence, in the control of venous return.

While much is known about the factors controlling cardiac function and systemic blood pressure under both physiologic and pathologic conditions, relatively little is known about the control of the venous circulation. Changes in the capacity of the peripheral circulation importantly influence cardiac performance through the Frank Starling mechanism.

The systemic venous system plays an important role in the regulation of ventricular filling. About two-thirds of the circulating blood volume resides within the systemic venous system in man [1]. Of the blood within the venous circulation, approximately two-thirds to three-fourths resides within the small veins and venules; the remainder is within the large veins [1]. The capacity of the arterial system and of the capillaries is relatively small. Unlike arterial resistance vessels, the capacitance vessels are affected little by local metabolic changes. The overall control of venous circulatory activity is mainly accomplished through autonomic nervous activity and circulating hormones [1].

Exclusive of the heart and lungs, the three major areas within the venous system which regulate blood volume are the cutaneous, skeletal muscle, and splanchnic circulations as illustrated in Fig. 1 [2]. The pumping action of skeletal muscle during exercise augments venous return to the heart by compression of skeletal muscle veins [3]. This increase in venous return results in an increase in cardiac output by the Frank Starling mechanism. While circulating substances such as drugs and catechol-

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amines may influence the capacity of the skeletal muscle venous system, sympathetic neural control of the venous system in this area is minimal [2]. The venous system of the skin can respond to sympathetic innervation and circulating substances, but this latter system is a relatively small reservoir consisting of only several hundred milliliters of blood [2].

The splanchnic circulation, however, is a rather extensive blood reservoir. In man, approximately one-fifth of the total blood volume resides within the splanchnic venous bed [2]. The areas within the splanchnic circulation which constitute this blood reservoir include the spleen, the mesenteric vasculature, and the sinusoids of the liver. The spleen has the potential of decreasing in size sufficiently to release as much as one-third of the splanchnic venous volume of blood into the remainder of the circulation [4]. The venous system of the mesenteric vasculature can contribute between one-third and one-half of the splanchnic volume to the central blood volume [4]. Lastly, the sinusoids of the liver are capable of releasing the remainder of the splanchnic blood volume into the rest of the circulation [4]. Thus, the splanchnic circulation has the capability of augmenting the central blood volume within the vena cava, the heart, and the lungs by 600–700 ml and is of great potential importance in the regulation of venous return in man.

It has been thought that the major mechanism of control of blood volume within the splanchnic circulation consists of an action directly on blood vessels by sympathetic innervation and circulating substances such as catecholamines [2]. A decrease in systemic arterial pressure is accompanied by a decrease in the inhibitory influences of the baroreceptors of the carotid sinus and aortic area on the vasomotor center and a resulting increase in sympathetic outflow. An increase in sympathetic stimuli results in a constriction of venous smooth muscle and mobilization of blood from the splanchnic vasculature toward the heart.

It has been established that alpha adrenergic receptor stimulation, whether secondary to increased sympathetic nerve activity or to circulating catecholamines, results in constriction of veins of numerous organ systems, including skin, skeletal muscle, and the kidney [2,5–10]. Alexander [11] has demonstrated that phenylephrine, an alpha adrenergic receptor stimulating agent, increases the tone of isolated segments of the mesenteric vasculature. Opdyke and Ward [12] have employed an
 exterioirized, continuously weighed canine spleen model, which is representative of an in situ segment of the portal circulation, to assess the effects of adrenergic stimulation on the splenic smooth muscle capsule. The administration of norepinephrine and epinephrine results in alpha adrenergic mediated splenic constriction in the dog, as manifested by a decrease in spleen weight, which is abolished following alpha receptor blockade with phentolamine.

Our recent preliminary data suggest that dobutamine, a new synthetic catecholamine recently developed as a therapeutic agent for the treatment of low cardiac output states, decreases canine spleen weight by means of alpha adrenergic receptor stimulation [13]. With the intravenous infusion of dobutamine (80 µg/min) in 15 anesthetized dogs spleen weight decreased 15 ± 3.8% (SEM) (p < .01) from a mean control weight of 245 g. This was associated with a modest (7 ± 2 mm Hg) decrease in mean aortic pressure and a small (12 ± 6 beats/min) increase in heart rate. The splenic constriction, however, could not be explained by a reflex mechanism, since dobutamine produced constriction of comparable magnitude after splenic denervation and adrenalectomy. Furthermore, intrarterial injections of dobutamine into the splenic artery (80 µg bolus) were associated with a decrease in spleen weight of 14 ± 1.5% (p < .001) from a mean control weight of 294 g without associated significant changes in mean blood pressure or heart rate. Alpha adrenergic receptor blockade with phenoxybenzamine entirely abolished the dobutamine induced decrease in spleen weight and uncovered a small, statistically insignificant increase in spleen weight. Thus, alpha adrenergic receptor stimulation, whether by circulating hormones or by therapeutic maneuvers, results in venoconstriction in the portal circulation.

It is likely that the venoconstrictor effects of alpha adrenergic receptor stimulation on both the splanchic and the remainder of the peripheral vasculature, exclusive of the heart, contributed to the increase in venous return noted by Kaiser, Ross, and Braunwald [6] when they administered phenylephrine to the dog on total cardiopulmonary bypass. However, in addition, this latter study demonstrated that beta adrenergic receptor stimulation by isoproterenol also resulted in an increase in venous return. This increase in venous return to the central circulation was blocked by pronethalol (Nethalide®), one of the first beta adrenergic receptor blocking drugs. In vivo studies of the effects of isoproterenol have clearly demonstrated the dilator properties of the drug in cutaneous veins, the femoral vein, and the vena cava through beta adrenergic receptor activation [15]. As recently reviewed by Shepherd and Vanhoutte [5] in isolated veins isoproterenol depresses spontaneous activity and depresses the responses to nerve stimulation or to vasoconstrictor drugs such as alpha adrenergic agonists. Both in the intact organism and in the organ bath, the venodilator action of isoproterenol is specifically counteracted by drugs known to block beta adrenergic receptors [5]. This venodilation should pool blood peripherally and not increase venous return to the heart as found by Kaiser et al. [6]. While it is true that very high doses of isoproterenol can cause alpha adrenergic receptor activation and contraction of isolated helical strips of canine saphenous veins, the concentration of isoproterenol necessary to produce this effect is 1 × 10^{-5} g/ml [14]. This concentration is at least 40 times that achieved by Kaiser et al. [6].

Thus, in the experiments by Kaiser, Ross, and Braunwald [6], the question remains as to the mechanism whereby beta adrenergic receptor stimulation with isoproterenol caused an increase in venous return. The doses of isoproterenol employed by Kaiser et al. were much lower than those necessary to produce venoconstriction through
alpha adrenergic receptor stimulation. Furthermore, it seems unlikely that isoproterenol produced venoconstriction due to beta adrenergic receptor stimulation. It is possible that reflex influences on venomotor tone could have resulted in alpha adrenergic receptor stimulation of the venous circulation and displacement of blood from the animal. However, the recent data of Imai et al. [16] make this explanation unlikely. In the latter experiments, elimination of the baroreceptor reflex of sinoaortic origin failed to modify the increase in venous return induced by the infusion of isoproterenol into the ascending aorta of the dog. Bilateral carotid sinus denervation and vagotomy did not alter the effect of isoproterenol on venous return.

The recent work of Green [17,18] again confirms the finding of an increase in venous return caused by isoproterenol and postulates a possible mechanism whereby venodilatation by this agent might increase venous return to the heart. Using an experimental dog model [19], Green developed evidence for the existence of an "effective splanchnic back pressure." In these experiments, which employed a right heart bypass preparation, Green demonstrated that elevations of hepatic venous pressure produce no change in splanchnic blood flow or portal pressure until hepatic venous pressure is raised to a critical value. As hepatic venous pressure is raised above this value, portal pressure rises and splanchnic flow falls. This critical value of hepatic venous pressure is therefore considered to be the "effective splanchnic back pressure" under conditions in which hepatic venous pressure is less than this value. Green's experiments [19] have demonstrated that the effective splanchnic back pressure generates volume in the splanchnic bed. Green noted [18] that isoproterenol reduced hepatic vascular resistance as determined by measurements of "effective splanchnic back pressure." Therefore, Green postulated that the increase in venous return produced by isoproterenol can be wholly or partially accounted for by a release in splanchnic blood volume caused by a reduction in the effective splanchnic back pressure. Thus, it is possible that the liver may, through changes in resistance to splanchnic outflow, act like a "sphincter" which can regulate the transfer of blood volume from the relatively high pressure system in the portal circulation to the central venous circulation. This concept is illustrated schematically in Fig. 2.

Since Green was not able to quantitate the effect of beta adrenergic receptor stimulation on the resistance to blood flow from the portal to the central circulation,

![Diagram](image)

**FIG. 2.** A schematic representation of the control of the splanchnic blood volume. See text for details.
our preliminary experiments [20] were undertaken to examine the effects of adrenergic receptor stimulation on venous return and on transhepatic resistance to portal blood flow. For this study, dogs were anesthetized with chloralose and urethane, vagectomized, ganglionically blocked, and placed on total cardiopulmonary bypass at 1.5 L/min. Isoproterenol (6 \( \mu \)g/min) and norepinephrine (30 \( \mu \)g/min) were infused for 10–24 minutes. Changes were noted in pump reservoir volume with the central venous pressure set at 3, 8, or 13 cm H\( _2 \)O. Isoproterenol caused a loss of blood of 20–150 (mean 80 ± 30) ml from the dogs (\( p < .05 \)) and norepinephrine a loss of 190–290 (mean 240 ± 30) ml (\( p < .05 \)). Selective adrenergic blockade with either phenoxybenzamine or propranolol or double blockade with both drugs revealed that the isoproterenol induced volume changes were mediated through beta adrenergic receptor stimulation, whereas norepinephrine induced volume changes were mediated through both alpha and beta adrenergic receptor stimulation. After the hepatic and mesenteric vasculature was ligated and hence removed from the circulation in two dogs, almost no change in reservoir volume was noted with isoproterenol or norepinephrine. These latter data localized the capacity effects of the two catecholamines primarily to the splanchnic vasculature in the dog. In the animals without mesenteric vascular ligation, isoproterenol and norepinephrine each resulted in a decrease of 7 ± 3 (\( p < .05 \)) cm H\( _2 \)O in portal venous pressure from a mean of 25 ± 4 cm H\( _2 \)O for isoproterenol and a mean of 27 ± 1 cm H\( _2 \)O for norepinephrine. In two of these animals, hepatic venous return was continuously monitored. With isoproterenol or with norepinephrine, hepatic flow increased while the pressure gradient from portal to hepatic vein decreased, indicating a fall in resistance to transhepatic portal outflow. Thus, isoproterenol, entirely, and norepinephrine, in part, each caused decreases in venous capacity by beta adrenergic relaxation of a portion of the venous circulation contained within the liver. This diminution of resistance to portal blood flow across the liver explains the apparent discrepancy of isoproterenol associated relaxation of isolated segments of the venous circulation [5,15] with the displacement of blood from the whole animal [6,16,17]. This mechanism of diminishing transhepatic vascular resistance may be of major importance in the regulation of venous capacity.

If the diminution of transhepatic resistance is an important factor in increasing venous return, then increasing transhepatic resistance may be important in diminishing the return of blood to the heart. The experiments described above examining the effect of adrenergic receptor stimulation on systemic capacity and transhepatic resistance have been carried out with infusions of beta adrenergic receptor agonists. Over the past 5 years, in studies on arterial resistance vasculature, we have established that acetylstrophanthidin (a rapidly acting aglycone digitalis preparation) and digoxin vasoconstrict in both skeletal muscle and the heart through a centrally mediated neurogenic alpha adrenergic receptor mechanism [21–24]. It is possible that digitalis may exert a neurogenic effect on the venous circulation as well. Ross, Braunwald, and Waldhausen [25] have demonstrated that the administration of large doses of acetylstrophanthidin to the dog on total cardiopulmonary bypass results in a decrease in venous return to the heart. This decrease in venous return appears to result from an increase in resistance to blood flow across the liver with a consequent increase in portal vein pressure and a pooling of blood in the mesenteric circulation. Venting of the portal vein in this animal preparation resulted in an increase in venous return from the animal to an external pump oxygenator which is likely due to a diffuse vеноconstrictor effect of the drug [26]. Our preliminary unpublished observa-
tions suggest that the increase in canine transhepatic resistance and the increase in portal vein pressure associated with ouabain (a digitalis glycoside) administration is, at least in part, mediated through alpha adrenergic receptor stimulation.

The magnitude of either dilation or constriction of a transhepatic "sphincter" may be importantly related to the control level of transhepatic resistance to portal blood flow. In our experiments on the effects of isoproterenol and norepinephrine mentioned above, the control levels of portal pressure were elevated for the dog [20], and therefore the absolute volume of blood displaced centrally with beta adrenergic receptor stimulation may have been greater than under conditions of an initially normal portal pressure. Explanations for the elevation of portal pressure should include the possibility of endotoxin release, which is known to elevate portal pressure in the dog [27]. This release of endotoxin may have occurred during the extensive surgical manipulation necessary to set up the preparation. However, the study on the effects of vasopressin cited below [28] demonstrates that it is also possible to lower substantially transhepatic resistance to blood flow when portal pressure is initially normal (7.2 ± 1 mm Hg).

A recently published study [28] on the effects of vasopressin on canine hepatic hemodynamics helps to localize the site of control of transhepatic resistance. The results from this study demonstrate that infusions of vasopressin into either the hepatic artery or the portal vein elicit hepatic venous dilation and a quantitatively similar decrease in portal vascular resistance. This suggests that these alterations in portal vascular resistance were due to effects on a common outlet resistance site. Thus, it appears that in addition to increasing arterial resistance and thereby decreasing inflow to the mesenteric circulation [28], vasopressin also reduces the resistance to portal blood flow at a site which is likely to be at or beyond the outlets of the hepatic sinusoids into the hepatic venules. These data, obtained in a different laboratory, support the concept of the existence of a hepatic venous "sphincter" which is of importance in regulating portal vein hemodynamics.

Hepatic venous sphincters are thought to be present in several animal species, including the dog [29-31]. Possible anatomic locations for the sphincters include the junctions of the hepatic veins with the inferior vena cava [32], the sublobular hepatic veins [33], and the hepatic sinusoids [34]. Alternatively, it is possible that the entire hepatic venous system may vasoconstrict [35,36].

In man, Popper [37] described the junctions of central venules with hepatic veins as being "funnel-like." Elias and Popper [38] noted that thin-walled hepatic venules in the human constricted on entering a thick-walled vessel. In neoprene casts of the hepatic venous system in man made by Gibson [39], the junctions of central venules and hepatic veins were sometimes retracted. Since the junctions were numerous, Gibson concluded that junctional constriction was probably the "chief venous sphincter mechanism in the human liver." Krogh and Lindhard [40] demonstrated that the human liver and portal vein bed could store and release blood and thereby control the rate of filling of the heart and thus cardiac output. These data have been interpreted by Knisely et al. [34] as indicating that the control of the outflow of blood from livers of healthy humans is an important factor in the control of cardiac output. Thus, it appears likely that the data obtained using the dog model will be at least directionally similar to those in man, but the extent to which post-sinusoidal resistance regulates transhepatic blood flow in the human remains to be documented.

The control of the total venous circulation exerts an important influence on cardiac filling and hence on cardiac output. The possible role of the liver as a
"sphincter" controlling the return of blood from the relatively high pressure portal system to the lower pressure central venous system may be a major factor in the regulation of the distribution of blood volume between the central and splanchnic vasculature in man. This regulation within the liver could importantly influence cardiac performance.

REFERENCES

1. Folkow B, Neil E: Circulation. New York, Oxford University Press, 1971, p 44
2. Shepherd JT, Vanhoutte PM: Role of the venous system in circulatory control. Mayo Clin Proc 53:247, 1978
3. Braunwald E, Ross J Jr, Sonnenblick EH: Mechanisms of Contraction of the Normal and Failing Heart. 2nd edition. Boston, Little, Brown and Company, 1976, pp 292-293
4. Horvath SM, Kelly T, Folk GE Jr, Hutt BK: Measurement of blood volumes in the splanchnic bed of the dog. Am J Physiol 189:573, 1957
5. Shepherd JT, Vanhoutte PM: Veins and Their Control. London, WB Saunders, Ltd, 1975
6. Kaiser GA, Ross J Jr, Braunwald E: Alpha and beta adrenergic receptor mechanisms in the systemic venous bed. J Pharmacol Exp Ther 144:156, 1964
7. Haddy FJ, Fleischman M, Emanuel DA: Effect of epinephrine, norepinephrine and serotonin upon systemic, small and large vessel resistance. Circ Res 5:247, 1955
8. Folkow B: Effects of catecholamines on consecutive vascular sections. Adrenergic Mechanisms. Boston, Little, Brown and Company, 1960, p 190
9. Mellander S, Johansson B: Control of resistance, exchange, and capacitance functions in the peripheral circulation. Pharmacol Rev 20:117, 1968
10. Aboud FM, Eckstein JW: Vascular responses after alpha adrenergic receptor blockade. II. Responses of venous and arterial segments to adrenergic stimulation in the forelimb of the dog. J Clin Invest 47:10, 1968
11. Alexander RS: The influence of constrictor drugs on the distensibility of the splanchnic venous system, analyzed on the basis of an aortic model. Circ Res 2:140, 1954
12. Odpkye DF, Ward CJ: Spleen as an experimental model for the study of vascular capacitance. Am J Physiol 225:1416, 1973
13. Fuchs RM, Rutlen DL, Powell WJ Jr: Effects of dobutamine on venous capacity. Clin Res 24:218A, 1976
14. Vanhoutte PM, Shepherd JT: Effect of cooling on beta receptor mechanisms in isolated cutaneous veins of the dog. Microvasc Res 2:454, 1970
15. Webb-Peploe MM, Shepherd JT: Beta receptor mechanisms in the superficial limb veins of the dog. J Clin Invest 48:1328, 1969
16. Imai Y, Satoh K, Ta帘 N: Role of the peripheral vasculature in changes in venous return caused by isoproterenol, norepinephrine, and methoxamine in anesthetized dogs. Circ Res 43:553, 1978
17. Green JF: Pressure-flow relationship in the peripheral circulation of the dog with isoprenaline. Clin Exp Pharmacol Physiol 2:181, 1975
18. Green JF: Mechanism of action of isoproterenol on venous return. Am J Physiol: Heart Circ Physiol 1:H152, 1977
19. Green JF: Pressure-flow and volume-flow relationships of the systemic circulation of the dog. Am J Physiol 229:761, 1975
20. Rutlen DL, Supple EW, Powell WJ Jr: Adrenergic regulation of venous circulation. Am J Cardiol 41:420, 1978
21. Stark JJ, Sanders CA, Powell WJ Jr: Neuromediated and direct effects of acetylstrophanthidin on canine skeletal muscle vascular resistance. Circ Res 30:274, 1972
22. Hamlin NP, Willerson JT, Garan H, Powell WJ Jr: The neurogenic vasoconstrictor effect of digitalis on coronary vascular resistance. J Clin Invest 53:288, 1974
23. Garan H, Smith TW, Powell WJ Jr: The central nervous system as a site of action for the coronary vasoconstrictor effect of digoxin. J Clin Invest 54:1365, 1974
24. Sagar K, Hanson E, Powell WJ Jr: Neurogenic coronary vasoconstrictor effects of acetylstrophanthidin and digoxin during acute global ischemia in dogs. J Clin Invest 60:1248, 1977
25. Ross J Jr, Braunwald E, Waldhausen JA: Studies on digitalis. II. Extracardiac effects on venous return and on the capacity of the peripheral vascular bed. J Clin Invest 39:937, 1960
26. Goldman M, Rutlen DL, Powell WJ Jr: Effect of ouabain on total systemic capacity and capacitance. Clin Res 26:234A, 1978
27. Reynolds DG, Swan KG: Intestinal microvascular architecture in endotoxic shock. Gastroenterology 63:601, 1972
28. Richardson PD, Withington PG: The effects of intraarterial and intraportal injections of vasopressin on the simultaneously perfused hepatic, arterial and portal venous vascular beds of the dog. Circ Res 43:496, 1978
29. Greenway CV, Stark RD: Hepatic vascular bed. Physiol Rev 51:23, 1971
30. Greenway CV, Oshiro G: Effects of histamine on hepatic volume (outflow block) in anaesthetized dog. Br J Pharmacol 47:282, 1973
31. Walker WF, MacDonald JS, Pickard C: Hepatic vein sphincter mechanism in the dog. Br J Surg 48:218, 1960
32. Bauer W, Dale HH, Poulsson LT, Richards DW: The control of circulation through the liver. J Physiol 74:343, 1932
33. Deysach LJ: The nature and location of the "sphincter mechanism" in the liver as determined by drug actions and vascular injections. Am J Physiol 132:713, 1941
34. Knisely MH, Harding F, Debacker H: Hepatic sphincters. Science 125:1023, 1957
35. Maegrith BG, Andrews WHH, Wenyon CEM: Active constriction of hepatic venous tree in anaphylactic shock: relation to centrilobular lesions. Lancet 2:56, 1949
36. Thomas WD, Essex HE: Observations on the hepatic venous circulation with especial reference to the sphincter mechanism. Am J Physiol 158:303, 1949
37. Popper H: Über Drosselvorrichtungen an Lebervenen. Klin Wschr 10:2129, 1931
38. Elias H, Popper H: Venous distribution in livers. Arch Path Lab Med 59:332, 1955
39. Gibson JB: The hepatic veins in man and their sphincter mechanisms. J Anat Lond 93:368, 1959
40. Krogh A, Lindhard J: The measurement of the blood flow through the lungs of man. Skand Arch Physiol 27:100, 1912