Escape of the Liver Vasculature From Adrenergic Vasoconstriction (36782)

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The phenomenon of autoregulatory escape has been described in several vascular beds (1–7), but only in cat small intestine has it been extensively studied (1, 5–7). Electrical stimulation of sympathetic nerves or infusion of norepinephrine results in an initial decrease in intestinal blood flow, which tends to be reversed if stimulation or infusion is continued over a period of several minutes. Accumulation of vasodilator metabolites (1), and activation of beta receptor sites (6), as well as other explanations have been presented. Although many studies have been done on autonomic responses of liver vessels, in only one has autoregulatory escape been reported. Greenway, Lawson and Mellander (2) have found in the cat liver pronounced escape of the hepatic arterial bed during electrical stimulation of the hepatic nerve and also report some observations on escape during hepatic arterial infusion of norepinephrine. The study presented here is a much more extensive investigation of this problem using an *in situ*, autoperfused canine liver preparation.

Methods. Dogs weighing 20 kg or over were anesthetized with sodium pentobarbital at an initial intravenous dose of 30 mg/kg. An incision was made below the right costal margin exposing the liver and major vessels of the upper abdomen. A region of the hilum of the liver was carefully dissected and an area of common hepatic artery and portal vein cleared. The hepatic nerve was ligated and cut. The gastroduodenal artery was doubly tied and sectioned between the most distal of the proper hepatic arteries and the origin of the right gastric artery. An intravenous dose of heparin (500 U/kg) was given at this time. The common hepatic artery was ligated, cannulated (PE 320 tubing) toward the liver, and then perfused from a femoral artery by way of a short length of 1/8 in. i.d. Silastic rubber tubing. An electromagnetic flow transducer and a lateral connection for measurement of perfusion pressure were inserted in this circuit. A jugular vein and the proximal stump of the splenic vein were then cannulated (PE 410 tubing) and connected by a length of 3/8 in. i.d. Silastic tubing. This provided a means for shunting portal flow directly into the systemic venous system when it was necessary to occlude portal inflow to the liver during cannulation of the portal vein and during zeroing of the portal flow transducer. With the extracorporeal shunt circuit open, the portal vein was ligated above its confluence with the splenic vein, and cannulated toward the liver. This cannula was connected to one arm of a Y-tube in the shunt circuit. An electromagnetic flow transducer was inserted in this portion of the system such that portal inflow to the liver would be measured when it was restored by clamping the shunt circuit between the Y-tube and the jugular vein cannula. The anterior pancreaticoduodenal vein was ligated and a catheter introduced until its tip came to rest within the hilum of the liver for measurement of portal venous perfusion pressure. Inferior vena cava pressure in the region of the hepatic vein orifices was also measured by a catheter which entered a femoral vein such that its tip came to rest at this site. Systemic arterial pressure in the abdominal aorta was likewise measured by way of a femoral artery.

Statham strain gauge transducers were used for pressure measurements and flows were measured with a Biotronex BL 410 electromagnetic blood flowmeter. Recording was on a Gilson macropolygraph. Drugs were

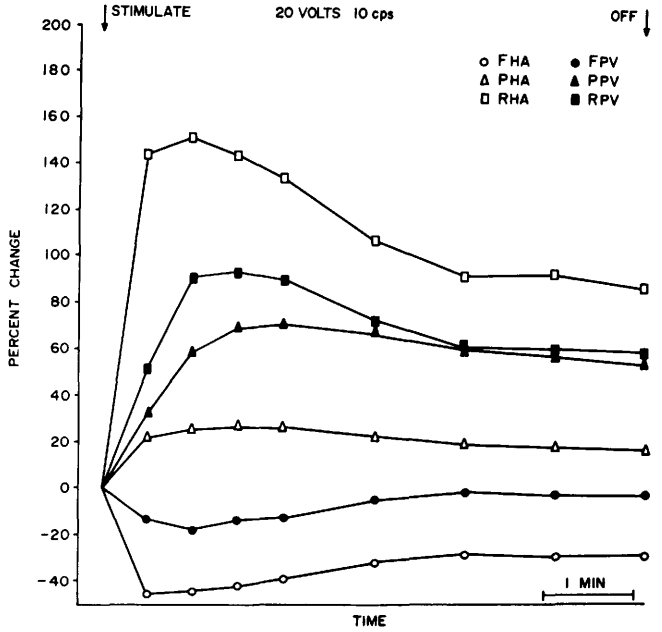

FIG. 1. Mean percentage change (33 experiments) in hepatic artery flow (F_{HA}), hepatic artery pressure (P_{HA}), hepatic artery resistance (R_{HA}), portal vein flow (F_{PV}), portal pressure (P_{PV}) and intrahepatic portal venous resistance (R_{PV}) at 0.5, 1.0, 1.5, 2, 3, 4, 5 and 6 min after onset of hepatic nerve stimulation.

prepared at the desired concentration in saline and infused into the hepatic artery, portal vein or femoral vein at a rate of 0.764 ml/min using a Harvard syringe pump. In one group of experiments a shielded electrode was attached to the peripheral end of the hepatic nerve trunk such that electrical stimulation could be applied with a Grass S48 stimulator.

Results. The effect of electrical stimulation (20 V, 10 cps, 10 msec duration) of the hepatic nerve trunk for periods of 5 min or longer was studied in a series of 33 experiments. This resulted in an initial decrease in liver blood flow and increase in hepatic arterial and portal venous pressure and resistance during the first 1 min stimulation. A tendency for recovery from vasoconstriction in both vascular beds of the liver was seen throughout the period of continued stimulation in all but 4 experiments. After cessation of the stimulus a transient overshoot in hepatic artery flow was seen. Mean percentage change in each parameter was calculated at several time intervals after the onset of stimulation and data summarized in Fig. 1. Between the 1 and 4 min intervals both arterial and portal resistance patterns are clearly indicative of escape from vasoconstriction to the extent of about 40%. In no case did escape begin prior to 1 min. However, one further finding came out of nerve stimulation studies. In 25 experiments the first 5 min control stimulation was followed by a second after a 2 min recovery period. Constrictor response was significantly ($p = 0.01$) less during the second stimulation period; full responsiveness not returning unless the recovery period was 10 min or longer. This leads us to suspect that part of escape as seen during stimulation might be due to some change in characteristics of the nerve or to depletion of neurotransmitter substance.

Effects of hepatic arterial (HA) infusion of norepinephrine at 5 different dose rates for periods of 20 min duration was studied in a series of 32 experiments. Hepatic artery resistance rapidly rose throughout the first 3 to 5 min infusion, and then either began to decline, possibly indicating autoregulatory es-

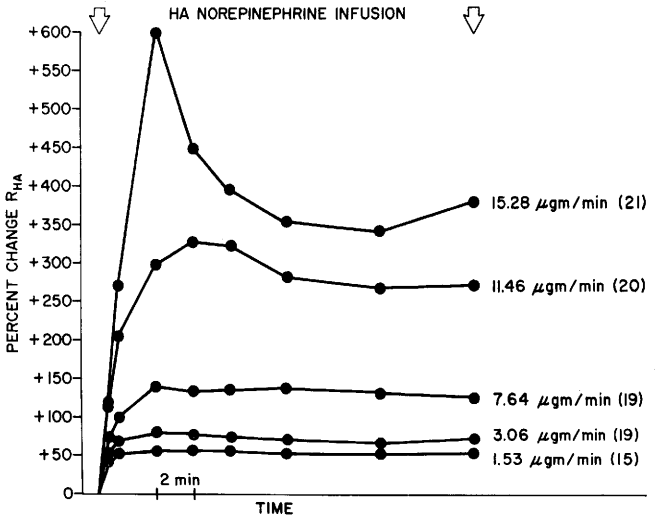

FIG. 2. Mean percentage change in hepatic artery resistance (R_{HA}) after 0.5, 1, 3, 5, 7, 10, 15 and 20 min of hepatic arterial norepinephrine infusion. Data from all trials at each dose rate in a total of 32 experiments are included.

cape, or continued to rise during the remainder of the 20 min period. As shown in Fig. 2, mean resistance increase was related to rate of infusion as was relative decrease in artery flow and increase in pressure. Hepatic arterial infusion at a rate of 7.64 μg/min was required to produce arterial resistance increases comparable to those seen during nerve stimulation; however, mean response showed only slight evidence of escape. Infusion at rates greater than this was required before mean artery resistance response as calculated and depicted in Fig. 2 showed any evidence of escape. In 11 experiments in which norepinephrine was given at a dose rate of 15.28 μg/min infusions were made not only by way of the hepatic artery but also into the portal vein (PV) and femoral vein (FV). In only about 60% of the experiments, under any circumstances, did artery resistance show any evidence of escape even after 20 min infusion.

Intraphepatic portal venous resistance, along with portal pressure, rapidly increased during the initial 5–6 min of infusion, after which they either declined or continued to rise throughout the 20 min infusion period. The increase in pressure and resistance seen during arterial infusion was directly related to dose rate. Portal flow was only slightly decreased (10% or less) in any case except during infusion into the femoral vein (15.28 μg/min) when a maximum decrease (mean $-15.2 \pm 1.5\%$) was reached during the first min and was followed by full recovery after 5 min indicating escape in the preportal bed under these circumstances. Greatest maximum increase in portal resistance (mean $+64.9 \pm 1.5\%$) was seen after 5 min infusion (15.28 μg/min) into the portal vein. This was somewhat less than that seen during electrical stimulation (see Fig. 1). As in the case of artery resistance, again in only about 60% of the total number of trials did portal venous resistance give any evidence of escape from constriction after 20 min infusion.

Another approach to presentation of the data is taken in Tables I and II. Mean of the maximum increase in resistance, reached during each trial sometime between 1 and 7 min of infusion, is given along with means of the corresponding relative changes in flow and pressure. This is compared with the mean resistance increase still existing after 20 min infusion. However, in this case, data included are from only those experiments in which arterial or portal resistance showed any evidence of escape.

Effects of alpha and beta adrenergic blocking agents on response to hepatic arterial

TABLE I. Summary of Hepatic Arterial Norepinephrine Infusions in Which Arterial Resistance (R_{HA}) Showed Any Evidence of Escape.

Dose (μg/min)	Route	Total trials	No. show escape	% ΔP_{HA} (mean ± SE)	% ΔF_{HA} (mean ± SE)	Max % ΔR_{HA} (mean ± SE)	% ΔR_{HA} at 20 min (mean ± SE)	Mean % recovery R_{HA}
1.53	HA	15	9	15.1 ± 1.1	−35.9 ± 2.6	81.9 ± 8.6	46.7 ± 7.5	43
3.06	HA	19	13	20.3 ± 1.4	−41.9 ± 3.1	106.3 ± 12.3	70.0 ± 9.3	34
7.64	HA	19	12	29.9 ± 3.2	−48.2 ± 3.8	174.0 ± 23.1	108.0 ± 11.6	38
11.46	HA	20	13	41.4 ± 1.9	−67.8 ± 4.0	462.4 ± 98.0	212.0 ± 32.0	54
15.28	HA	21	13	44.4 ± 5.6	−71.2 ± 6.5	822.0 ± 207.9	337.0 ± 80.1	59
15.28	PV	23	10	29.4 ± 5.5	−31.7 ± 4.7	99.1 ± 18.8	66.0 ± 17.1	33
15.28	FV	16	11	49.2 ± 7.4	−16.9 ± 5.6	89.4 ± 16.8	75.8 ± 15.3	15

infusion of norepinephrine were also studied. Doses of dibenamine used were in the range of those required to prevent decrease in hepatic artery flow during electrical nerve stimulation, while dose of propranolol used was comparable to that required to prevent an increase in hepatic artery flow following isoproterenol injection. In 8 experiments dibenamine (20 mg/kg) was infused into the hepatic artery 30 min prior to a 11.46 μg/min norepinephrine infusion. Vasoconstriction was abolished in both vascular beds of the liver. In fact, vasodilation was seen in the arterial vessels in 7 experiments and in the portal bed in 3 experiments. Mean changes in arterial and portal resistance at 20 min were -21.0 ± 2.1 and $+2.2 \pm 7.7\%$, respectively. Similarly, in another 8 experiments a 11.46 μg/min dose of norepinephrine was repeated 30 min following hepatic arterial infusion of propranolol (1 mg/kg). Arterial vasoconstrictor response was significantly greater ($p < .02$) than control throughout the entire 20 min infusion period after pretreatment with this beta blocking agent. There was a threefold increase ($p < .01$) in the mean maximum resistance response. In experiments in which artery resistance showed an evidence of escape from effects of norepinephrine infusion, this phenomena persisted after propranolol to about the same extent that it could be detected under control conditions. Mean response of intrahepatic portal resistance to norepinephrine was also greater than control after propranolol; however, the difference did not prove to be significant in terms of the standard t test ($p > .05$).

Discussion. Evidence of autoregulatory escape from vasoconstriction produced by sustained autonomic stimulation has been reported in cat small intestine (1, 5–7), colon (4), spleen (3) and liver (2). We have investigated this phenomenon in considerable detail using a canine liver preparation. Partial escape (mean 40% recovery) of the hepatic artery from vasoconstrictor action of nerve stimulation was seen in about 90% of the trials; however, usually only after about 5–6 min stimulation as compared with 14 to 100% recovery after 2 min reported by Greenway, Lawson and Mellander (2) in cat liver. Behavior of the portal bed was similar

in both studies except that we found a decrease in portal flow at onset of stimulation rather than an increase or no change. It also became apparent that responsiveness to electrical stimulation declined when a second stimulus was applied sooner than 10 min following an initial test stimulus. This finding, along with variability of the response speaks against prolonged faradic stimulation of nerves as a reliable experimental approach to collecting quantitative data on autonomic responses of the vasculature. Therefore, infusion of autonomic agents appears to be more suitable in the investigation of autoregulatory escape.

Infusion of norepinephrine by way of the hepatic artery, portal vein or femoral vein resulted in an increased vascular resistance in both beds of the liver to an extent directly related to rate of infusion. Infusion directly into the hepatic artery at a rate of 15.28 μg/min produced a response in this bed several times the mean increase in artery resistance of about 75% seen when drug was given at this rate by either of the other two routes. Maximum response of portal venous resistance to this dose rate was about the same (ca. + 60%) when administration was by either hepatic artery or portal vein. Mean maximum portal resistance increase was less than 10% when infusion was by way of the femoral vein. During hepatic arterial infusion drug is known to reach the intrahepatic portal venous vessels by way of arterial–portal communications (8) as well as by recirculation.

Behavior which might be described as autoregulatory escape did appear to occur in both vascular beds of the dog liver during 20 min periods of norepinephrine infusion; however, it was seen in only about 60% of the experiments. The reason for this is not clear. Data are included from only those animals in which control conditions remained stable and systemic arterial pressure was in excess of 100 mm Hg. In a previous study (9) using this dog liver preparation, autoregulation of hepatic arterial flow was seen during pressure–flow studies also in only about 60% of the experiments. Thus, autoregulatory escape like autoregulation itself, is not a constant finding; however, Richardson and Johnson (5) have shown in cat small intestine that

TABLE II. Summary of Hepatic Arterial Norepinephrine Infusions in Which Portal Venous Resistance (R_{PV}) Showed Any Evidence of Escape.

Dose (μg/min)	Route	Total trials	No. show escape	% ΔP_{PV} (mean ± SE)	% ΔF_{PV} (mean ± SE)	Max % ΔR_{PV} (mean ± SE)	% ΔR_{PV} at 20 min (mean ± SE)	Mean % recovery R_{PV}
1.53	HA	15	9	11.2 ± 2.3	−3.6 ± 1.6	13.2 ± 1.9	4.5 ± 2.1	66
3.06	HA	19	11	19.4 ± 7.8	−6.0 ± 1.9	17.7 ± 5.3	7.8 ± 4.2	56
7.64	HA	19	14	27.3 ± 5.7	−10.7 ± 2.6	31.6 ± 5.9	18.6 ± 4.6	41
11.46	HA	20	11	52.4 ± 11.9	−5.7 ± 1.7	40.1 ± 3.8	28.5 ± 3.7	29
15.28	HA	21	10	47.1 ± 4.6	−4.8 ± 2.2	69.2 ± 12.8	54.6 ± 13.1	21
15.28	PV	23	17	67.0 ± 6.5	−4.0 ± 1.4	74.9 ± 7.5	55.5 ± 7.5	26
15.28	FV	16	10	12.7 ± 6.5	−3.7 ± 2.9	19.3 ± 4.3	9.4 ± 2.8	51

the two events may occur independently.

Work done on autoregulatory escape in intestine has given rise to several hypotheses as to mechanisms involved. Ross (6) gives evidence that it is in part a result of activation of beta receptors. Others (1) have suggested vasodilation due to accumulation of metabolites. When the vascular bed of liver or intestine is subjected to sustained sympathetic stimulation net effect at any given time is a summation of forces tending to constrict and those tending to dilate. Stimulation of alpha receptors favors constriction while dilation (8, 10) and possibly increased metabolism (2) are promoted by beta stimulation. Further dilation may subsequently result from metabolite accumulation.

Although no clear explanation of mechanisms responsible for autoregulatory escape in liver can be given at this time the present study has pointed out several aspects. Failure of propranolol to significantly affect the escape response does not favor vasodilation by way of beta receptor stimulation as a major factor. Examination of data from those experiments alone in which vascular resistance showed evidence of escape to any extent after 20 min norepinephreine infusion (see Tables I and II) does, however, at least point in the direction of the metabolic hypothesis. Escape was most evident (mean 59% recovery) during hepatic arterial infusion at 15.28 μg/min when mean maximum increase in artery resistance was 822 and mean corresponding decrease in flow was 71.2%. It was least evident (mean 15% recovery) during femoral venous infusion when mean decrease in artery flow was only 16.9% and the maximum decrease in flow usually was reached only after 20 min infusion. Degree of escape appears generally to relate to extent and duration of flow loss and hence, metabolite accumulation; however, there is no clear-cut relationship here. In opposition to escape are forces of vasoconstriction which are directly related to the concentration of norepinephrine presented to the vascular bed in question. This becomes somewhat evident in response of intrahepatic portal venous vessels to hepatic arterial infusion (see Table II) where intensity of vasoconstriction also increased with dose rate; however, degree of escape decreased since reduction in portal flow was relatively slight at any dose. In the last analysis, the case for autoregulatory escape in canine liver, as presented in this study, is not as convincing as that provided by other data describing the response in cat intestine (1, 5–7) and cat liver (2). Partial recovery, which we have seen in some cases after prolonged norepinephrine infusion, could very possibly be due to some mechanism (tachyphylaxis to norepinephrine) quite different from that responsible for autoregulatory escape described in studies cited above.

Finally, response of hepatic arterial vessels to norepinephrine following pretreatment with dibenamine or propranolol (see Results) supports the presence of both alpha (constrictor) and beta (dilator) receptors in this vascular bed which is in agreement with most other findings (2, 5). Results would tend to support a similar situation with respect to intraphepatic portal venous vessels; however, more convincing evidence is still required to definitely establish presence of beta sites here.

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