Splanchnic Hemodynamics as Influenced by Hepatic Ischemia.* (22055)

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Certain hemodynamic observations made during a previous investigation in this laboratory(1) have shown that hepatic ischemia is followed by a vasodepressor response. The pertinent observations were a marked decrease in arterial pressure accompanied by elevation of portal venous pressure following 1 to 2 hours of complete hepatic ischemia. It was postulated in the preliminary paper that these manifestations could be attributed, in part at least, to hyperemia of the intestinal vasculature. Dilatation in the mesenteric circulation could cause, or contribute to the increase in portal pressure, and secondly, favor splanchnic pooling of blood which would contribute to the fall in arterial pressure.

The purpose of the present investigation was to study the portal circulation following complete hepatic ischemia of 2 hours' duration. Arterial, portal venous, and inferior vena cava pressures were measured with optical manometers concurrently with direct measurement of portal blood flow, so that hemodynamic calculations pertaining to vascular resistance changes could be made.

Methods. Experiments were conducted on 12 mongrel dogs anesthetized with 30 mg/kg of sodium pentobarbital intravenously. A midline incision was made followed by splenectomy. Residual splenic blood was drained into a heparin solution, filtered and reinfused into animals before beginning the experiment. A brass cannula of suitable size was inserted into the splenic vein until tip was near junction with portal vein. This cannula was connected by tygon tubing to a T-tube, one arm connected to a Gregg optical manometer (B), the other to inflow side of a Shipley-Wilson rotameter(2) (D in Fig. 1). The outflow side of rotameter was connected to a cannula introduced into the external jugular vein. A loose ligature was placed around portal vein as close to the liver as possible. This ligature was led out through brass tubing at E. Catheter (F) attached to manometer C was introduced via femoral vein into the inferior vena cava at level of diaphragm. This pressure was taken for hepatic venous pressure in some of the hemodynamic calculations. The other femoral vein was cannulated for infusion of fluids, additional anesthetic, and anticoagulant. Carotid blood pressure was measured with manometer A. The common hepatic artery was freed of investing tissue and nerve fibers, so that an occluding ligature could be passed around it. Care was taken not to interrupt the nerve fibers, and the ligatures were placed so as to lie between nerves and artery. The gastro-duodenal branch was ligated to minimize retrograde flow into the liver during

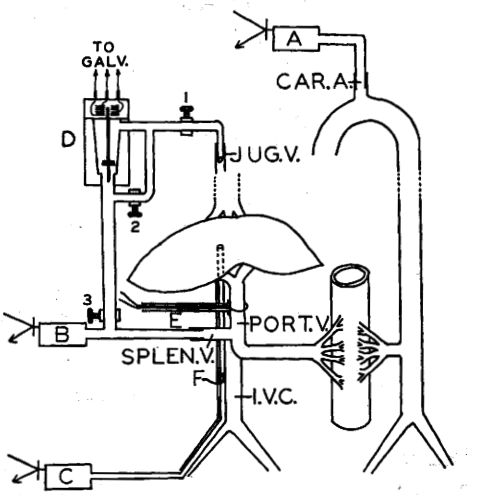

FIG. 1. Details circuit for measuring mesenteric blood flow. A, B, C: Optical manometers for measuring carotid arterial pressure, portal venous pressure, and inferior vena cava pressure respectively. D: Optically recording rotameter. E: Metal tube for ligature which occludes portal vein. Clamp 1 adjusts pressure in external circuit to agree with that registered in portal vein through cannula in splenic vein. Clamp 2 opens rotameter shunt circuit when necessary. Clamp 3 is opened when ligature at E is pulled taut, so that mesenteric blood flow is shunted into external circuit and the rotameter.

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TABLE I. Effect of Hepatic Ischemia on Splanchnic Hemodynamics.

Exp. No.	MABP, mm Hg			Flow, ml/min.†			R_M‡			PVP,§ cm/saline			HR§		
	A*	B*	%	A	B	%	A	B	%	A	B	%	A	B	%
1	116	95	−18	132	148	+12	.81	.58	−28	13.4	13.2	− 1	186	158	−15
2	148	92	−38	219	256	+17	.62	.32	−48	13.8	12.7	− 8	172	124	−28
3	158	138	−13	254	277	+ 9	.58	.46	−20	13.3	13.1	− 2	228	182	−20
4	138	142	+ 3	224	212	− 6	.57	.63	+11	13.7	14.3	+ 4	150	143	− 5
5	153	127	−17	159	161	+ 1	.88	.71	−20	17.8	17.0	− 4	200	177	−12
6	163	136	−17	188	190	+ 1	.85	.68	−20	12.2	12.2	0	209	197	− 6
7	162	150	− 7	207	157	−24	.74	.87	+18	15.7	16.1	+ 3	170	150	−12
8	160	155	− 3	208	191	− 8	.73	.77	+ 6	11.3	12.8	+13	212	190	−10
9	169	151	−11	137	110	−19	1.25	1.28	+ 3	14.8	14.1	− 5	182	160	−12
10	132	114	−14	243	183	−25	.51	.59	+16	12.0	10.5	−13	172	137	−20
11	161	159	− 1	259	262	+ 1	.58	.53	−10	13.2	15.3	+16	162	151	− 7
12	129	116	−10	183	173	− 6	.67	.64	− 5	9.1	9.2	+ 1	153	161	+ 5
Avg			−12			− 4			− 8			+.3			−15

* A, values before ischemia. B, values during final 30 min. of 2-hr ischemia.

† Flow does not include splenic contribution to portal vein.

‡ R_M = Mesenteric resistance, calculated from the ratio: $\frac{\text{MABP} - \text{PVP}}{\text{Flow}}$.

§ PVP = Portal venous pressure. HR = Heart rate.

ischemic period. Prior to beginning of experiment the animals were given a total dose of 40 mg heparin and 85 mg of a heparinoid (Manuronate); maintenance doses were continuously infused thereafter. The following method was used to measure *portal blood flow* preceding and following the period of hepatic ischemia. Portal venous pressure was noted immediately preceding each flow determination. The external circuit was then opened at clamp 3, and the ligature around the portal vein was pulled taut, occluding the vein against the brass tubing, E. The portal blood then flowed through the splenic cannula and the external circuit and rotameter into the jugular cannula. The caliber of tubing in external circuit was adjusted by clamp 1 so that pressure was maintained at exactly the same level as the portal pressure prior to manipulation, *i.e.*, while perfusing the liver. After stabilization, flow and pressures were recorded, then the circuit was closed and blood recirculated through the liver. The above procedure required less than a minute. Records were made at 2-3 minute intervals for an average time of 25 minutes. All flow and pressure measurements were made during the expiratory pause. Zero pressure reference was at the level of the inferior vena cava. No correction was made for intra abdominal pressure under the assumption that it would be approximately equal to the atmospheric pressure with the open abdomen. After initial flow and pressure measurements were made, the hepatic artery was closed and portal ligature at E pulled taut, so that portal blood was continuously diverted through the external shunt circuit for the 2 hour period of ischemia. Pressure in this circuit was kept at approximately the initial portal pressures with the aid of clamp 1. Flow measurements during the period of ischemia were made with continuous flow through the rotameter. Upon release of the occluding ligatures, flow measurements were resumed at first at 1-2 minute, later at 3-5 minute intervals, in the manner used prior to ischemia. Observations were usually continued for about one hour. During and following hepatic ischemia, glucose solution was continuously infused intravenously at the rate of 150 mg/kg/hr with a motor driven syringe.

Results. It is pertinent to present the hemodynamic changes which occurred during the 2 hour period of hepatic ischemia. The information is supplied in Table I, where mean arterial blood pressure, portal venous pressure, heart rate, portal blood flow, and mesenteric vascular resistance during the pre-ischemic period are compared with those obtained in the last half-hour of hepatic ischemia. Portal pressure was maintained at a constant value during the period, but all other functions

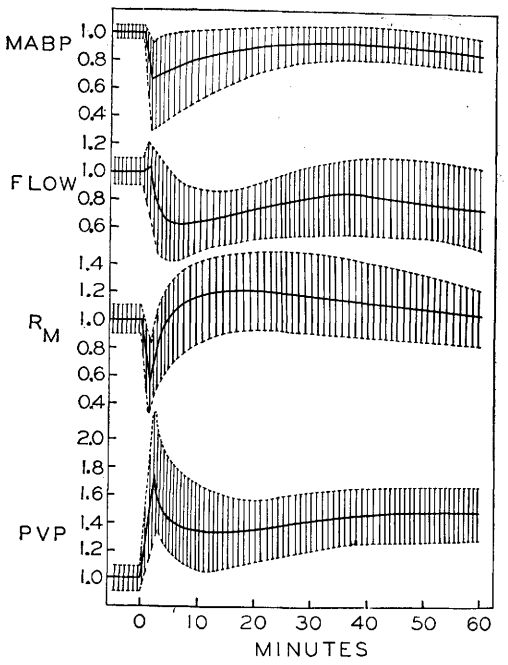

FIG. 2. Splanchnic hemodynamics following 2 hr of hepatic ischemia. Zero time coincides with time of release of ligatures occluding hepatic artery and portal vein. Solid line is avg trend of 8 experiments, expressed as ratios to function during the last 30 min. of the ischemic period. Dashed lines are drawn to indicate range of variation in this group of experiments and encompass *ca* 90% of all observations. MABP: mean arterial (carotid) blood pressure. Flow: portal (mesenteric) flow. PVP: portal venous pressure. R_M: mesenteric vascular resistance, calculated from the ratio

$$\frac{\text{MABP} - \text{PVP}}{\text{Flow}}.$$

showed a tendency to decline by the following average values: arterial pressure, −12%; heart rate, −15%; blood flow −4%; and mesenteric resistance −8%. It was decided for greatest accuracy to compare post-ischemic manifestations with measurements made in the 30 minute period immediately preceding release of occluding ligatures. These values will serve as control values for the experimental changes induced by hepatic ischemia. A total of 8 experiments showed essentially comparable results. These experiments are summarized in Fig. 2 which shows the mean trends following ischemia as ratios to the 30 minute period immediately preceding release of the ischemia.

Mean Arterial Blood Pressure. This decreased rapidly upon release to 66% of the control in 1½ minutes. A gradual restoration of blood pressure followed, and at 35 minutes it had returned to 93% of control. Thereafter, a second downward trend ensued, so that pressure was 86% of control at end of the hour. In several animals which were followed beyond the hour, the downward trend was seen to continue, but in this series none was followed long enough to determine ultimate survival.

Portal blood flow. This showed a momentary tendency to increase during the first 1½ minutes, during which interval blood pressure was rapidly falling. However, flow soon decreased, reaching a value of 63% of control, 6 minutes after restoration of hepatic blood flow. It then gradually increased, attaining a maximal value of 86% of control at 35 minutes. Thereafter it decreased to 75% of control at 60 minutes.

Mesenteric resistance. This showed its greatest decrease 1½ minutes after release, when it was 56% of control, coinciding with the time of most marked decline of arterial pressure. This suggested that the fall in arterial pressure was caused by peripheral vasodilatation in which the mesenteric vessels participated. It is presumed that the drop in arterial pressure initiated compensatory vasomotor reflexes to cause reversal in blood pressure trend. Apparently, participating in compensatory vasomotor reflexes was the intestinal vasculature, for its resistance increased within 15 minutes to 21% above control, during which time arterial pressure showed its maximal rate of recovery. Subsequently, mesenteric resistance decreased somewhat, accompanying the secondary decline in arterial blood pressure.

Portal venous pressure. This increased abruptly on release of the portal vein ligature, attaining a maximal value of 75% above control during the brief period of minimal mesenteric resistance. It remained continuously elevated, however, at a somewhat lower value during remainder of experiment.

Heart rate. This showed no striking change in post-ischemic period, averaging 97% of control for the entire series. One dog, however, decreased to the range 73-87% of control for 14 minutes post-ischemia. In another,

heart rate decreased to 85% of control during the interval 4 to 11½ minutes post-ischemia. It is believed, however, that generally heart rate changes are non-contributory to changes in blood pressure. Four animals showed atypical results. One (Exp. 12) never attained a blood pressure higher than 65 mm Hg after ischemia, and died within 15 minutes after release of the ligatures. Portal pressure increased to 18.3 mm Hg, and mesenteric resistance averaged *ca* half the control value during the brief period of post-ischemia. Another (exp. 9) also failed rather soon; 30 minutes after restoration of hepatic circulation arterial pressure started a rapid decline, with concomitant decrease in mesenteric resistance indicating failure of compensation. Two other animals (Exp. 10 and 11) showed continuously increased resistance and reduced blood flow; no phase of reduced resistance could be detected following release of occluding ligatures. Blood pressure was well maintained in both. In these two, either a vasodepressor response was not produced by the liver ischemia or compensation was so rapid and complete as to be undetectable by our method of measurement.

Discussion. The transient phase of reduced mesenteric vascular resistance following restoration of the hepatic circulation attests to the probability that vasodilatation is a contributing component to the initial precipitous collapse of arterial pressure. The extent to which other vascular circuits participate in the response is not presently known. Two alternative mechanisms may be involved: activation of a vasodilator reflex, or release of vasodilator material from the anoxic liver. In consideration of possibilities of a vasodilator reflex, Alexander(3) has noted reflex mesenteric venous dilatation associated with pressure elevation in the inferior vena cava of dogs, but vena cava pressure in the present series showed no significant change following hepatic release. The possibility that increased portal venous pressure would initiate a vascular reflex was investigated(4), but no mesenteric dilatation was observed. Johnson(5) has noted a transient phase of reduced hepatic resistance immediately following transfusion after prolonged hypotension in rats, and has suggested that this may be a dilator reflex in response to elevation in arterial pressure when blood was re-infused. In our investigation, dilatation appeared to be localized in the mesenteric vessels, and concurrently hepatic resistance was increased.

The alternative mechanism, that a vasodepressor substance is released by the anoxic liver, is herewith favored, although based on circumstantial evidence. At present the nature of such a substance is speculative. VDM (vasoactive ferritin) had been proposed by Shorr *et al.*(6) as the vasodilator substance released by liver during anoxia of that organ, but conceivably other metabolites with vasodilator properties might be released in abnormal amounts following hepatic ischemia. Presenting difficulty to the hypothesis that a vasodilator substance is released by the anoxic liver is the fact that the organ itself apparently does not manifest hyperemia after 2 hours of ischemia. But vasomotor responses might be obscured by mechanical obstruction to flow incurred by the ischemia, *e.g.*, edema and swelling of hepatic lobular cells, with compression of the sinusoids.

The coincidence of the phase of reduced mesenteric resistance with the initial period of marked increase in portal pressure demonstrates that this hyperemia contributes to the observed elevation of portal venous pressure. But it is obvious that this is not the only factor—indeed, it may be a minor one—in sustained elevation of portal pressure, which remains elevated while mesenteric resistance is increased and intestinal inflow into the portal vein is reduced. The conclusion follows that the significant factor in elevation of portal pressure following hepatic ischemia is a sustained increase in resistance to portal inflow. If hepatic resistance is calculated from the ratio:

$$\frac{\text{portal pressure—inferior vena cava pressure}}{\text{portal flow}}$$

the ratio increases from 0.026 (.016–.039) (pre-ischemia) to 0.067 (.027–0.114) (post-ischemia) in 6 experiments of this group in which inferior vena cava pressures were measured. The latter pressure is taken as representative of hepatic venous pressure.

The compensatory reflexes which restore arterial pressure following initial collapse probably involve carotid and aortic pressoreceptors. In addition, it has been observed that elevation of portal pressure will itself cause mesenteric resistance to increase(4) by unknown mechanisms. The rapid institution of compensatory mechanisms makes it difficult to assess the true intensity and duration of the hepatic dilator action. The incomplete recovery of arterial pressure despite sustained increase in mesenteric resistance above the control value could be interpreted to mean that the influence of the hepatic depressor mechanism persists longer than the brief period of overt hyperemia indicates. The period of hyperemia could represent a phase of pooling and trapping of blood in capillaries and venules of the intestines (and possibly elsewhere), where it might remain segregated from active circulation, even though compensatory constriction of arterioles had supervened.

Hyperemic responses following anoxia and brief ischemia in other organs is a commonly observed phenomenon, but only a few illustrative examples can be cited here: coronary circulation(7,8), cerebral circulation(9), skin and muscle(10,11). It is generally opined that some metabolic substance having vasodilator properties is released in increased amounts as the result of anoxia to produce hyperemia, but the exact nature of the dilator substance is still a matter of speculation. Possibilities that have been invoked include the adenine nucleotides(12), histamine(10), and acetylcholine(8). When ischemia of the hind limb is prolonged (5-6 hours), renewal of circulation leads to circulatory collapse, the so-called "ischemic compression" shock (for refs. see (13)), presumably as the result of release of vasodepressor substances of a toxic nature by the ischemic limb.

Summary. The influence of complete hepatic ischemia of 2 hours' duration on arterial blood pressure, portal vein pressure, heart rate, and mesenteric vascular resistance was investigated in dogs. During ischemia, small gradual decreases occurred in arterial pressure, heart rate, portal blood flow and mesenteric resistance. On release of the occluding ligatures on the hepatic artery and portal vein, the following changes were observed: an immediate sharp decrease in arterial blood pressure; a brief period of increase in portal blood flow, followed by a decline; a sharp increase in portal venous pressure, and a marked decrease in mesenteric vascular resistance. These manifestations lasted approximately 5 minutes, and were then followed by a partial recovery of arterial pressure and portal blood flow, some reduction of portal venous pressure, and a significant increase in mesenteric resistance. Heart rate showed no significant change.

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