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Pressure Gradients in the Splanchnic Bed of the Monkey During Hemorrhagic Shock.* (27705)

EWALD E. SELKURT AND CARL F. ROTHE

Department of Physiology, Indiana University School of Medicine, Indianapolis, Indiana

In reviewing the comparative physiology of experimental shock, Zweifach(1) has called attention to the paucity of information for primates. The imperative need for treatment of the human in shock has greatly limited the study of physiological mechanisms in this species, and very few data are available in other primates. The purpose of the present investigation was to gain information on the behavior of the splanchnic circulation of the monkey during a standardized hemorrhagic shock procedure.

Methods. Eight squirrel monkeys (*Chrysothrix sciurea*) of both sexes, averaging 635 g in weight were used. Under pentobarbital anesthesia (35 mg/kg, I.P.), laparotomy permitted placement of a fine-bore polyethylene catheter into the portal vein *via* an intestinal vein tributary. *Via* the jugular vein, another catheter was positioned at the juncture of the hepatic veins and the inferior vena cava. A carotid artery was also catheterized. Pressures were simultaneously recorded with Statham transducers on an Offner recorder. Zero pressures were corrected to the level of the thoracic vena cava at the conclusion of the experiment. In 2 experiments, portal blood flow was measured with a low resistance bubble flow meter after adequate heparinization. Heart rate was measured from a lead II ECG tracing. Respiratory rate was recorded with a force transducer attached to the thorax, or computed from respiratory variations in the venous pressure tracings. Rectal temperature was continuously monitored, and body temperature was kept as constant as possible with the aid of a heat lamp.

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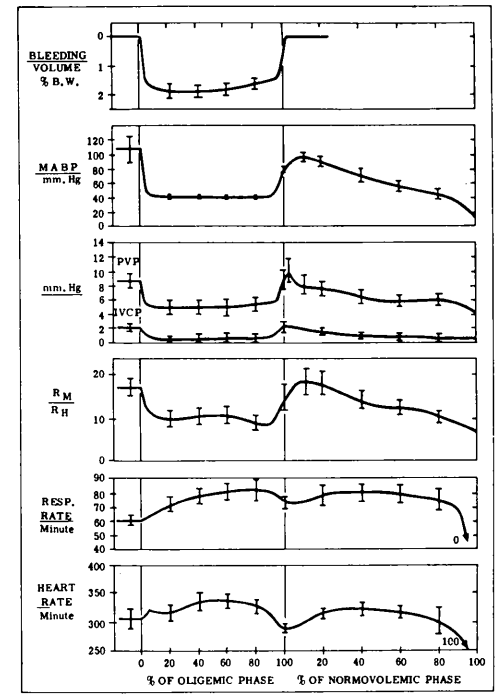
The hemorrhagic shock procedure was to bleed from an artery (carotid or femoral) into an overhanging reservoir whose height was adjusted to maintain the mean arterial blood pressure at 40 mm Hg. This was kept at the desired level until the animal had taken back 30% of the bleeding volume from the reservoir. At this time, the remainder of the blood was returned, and the post-transfusion events were followed until demise of the animal.

Results. Duration of the oligemic phase averaged 2 hours, and the normovolemic phase following transfusion 2 hours, 25 minutes (for range of values, see footnote, Table I). Results are given in Fig. 1 and Table I in relation to percentage duration of the oligemic and normovolemic phases.

Effects of hemorrhage: Oligemic phase. Fig. 1 shows the average trends obtained in 6 animals in which portal flow was not measured. The top curve shows the bleeding volume, which at the maximum averaged 1.9% of body weight. Below the curve depicting the arterial pressure appear the related trends in portal vein and inferior vena cava pressure. Following hemorrhage, the respective pressures decreased to 37, 58 and 25% of control.

The fourth panel of the figure shows the change in R_M/R_H ratio (mesenteric/hepatic vascular resistance). Changes in this ratio give insight to the relative resistance changes in the splanchnic bed. This was achieved by the method of vertical analysis employed by Wiggers, Opdyke, and Johnson(2) in the canine splanchnic bed during hemorrhagic shock. R_M is taken as $(P_A - P_{PV})F_1$, where



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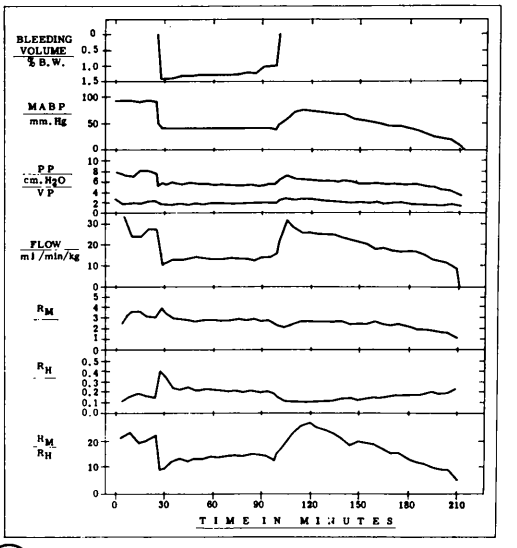

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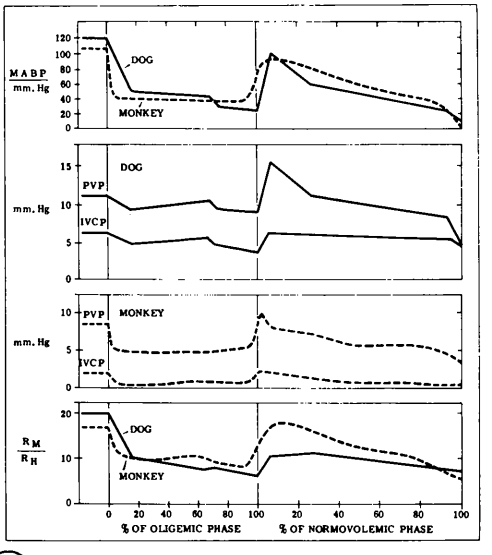

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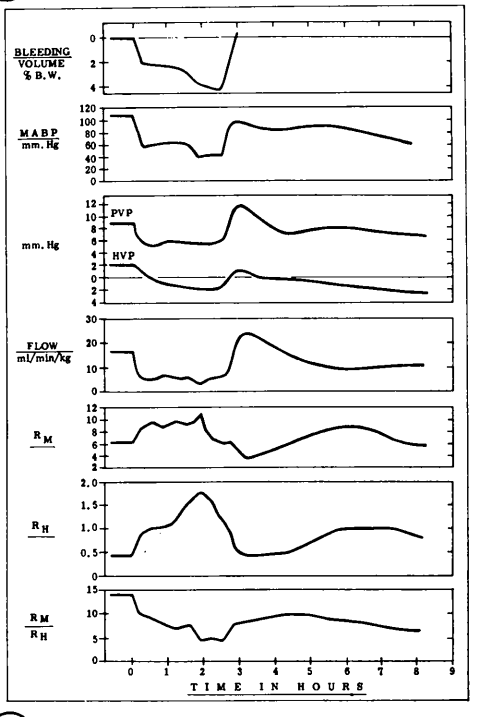

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FIG. 1. Mean trends with S.E. in 6 experiments of splanchnic vascular pressure gradients, respiratory rate, and heart rate during oligemic and normovolemic shock in the monkey. MABP: mean arterial blood pressure; PVP: portal venous pressure; IVCP: inferior vena cava pressure. R_M/R_H: ratio of mesenteric over hepatic vascular resistance.

FIG. 2. Representative experiment in a monkey in which portal flow was measured.

FIG. 3. Comparison of blood pressure gradients during hemorrhagic shock in monkey (dashed curves, avg of 6 exp. shown in Fig. 1), with dog (solid curves, representing mean trends of 6 exp. in the dog). (See ref. 2.)

FIG. 4. Representative experiment in the dog showing alterations in splanchnic hemodynamics during hemorrhagic shock. HVP: hepatic vein pressure; other symbols as in Fig. 1.

F_1 is flow through the intestinal and splenic circuits. R_H is the ratio: $(P_{PV} - P_{HV})F_2$, where F_2 is the flow contributed by the portal vein. (Inferior vena cava pressure is assumed to be a close approximation of hepatic vein pressure H_V and is used interchangeably.) R_M/R_H then equals: $\frac{(P_A - P_{PV})}{F_1} \Big/ \frac{(P_{PV} - P_{HV})}{F_2}$. Under stabilized conditions, F_1 should equal F_2, and by cancellation of F_1/F_2, $R_M/R_H = (P_A - P_{PV})/(P_{PV} - P_{HV})$. A decrease in the ratio could be the result of a decrease in mesenteric resistance, increase in hepatic resistance, or both. Since contrary changes are unlikely, a decrease in the ratio suggests a predominant increase in hepatic resistance. An increase in the ratio R_M/R_H conversely would indicate increase in mesenteric resistance, decrease in hepatic resistance, or both.

Following hemorrhage in the monkey, R_M/R_H decreases (Fig. 1, 2). Since it is unlikely that R_M diminishes, it can be inferred that there is a preponderant increase in R_H. This is supported by direct calculation of R_M and R_H, whose values are shown in Fig. 2.

On transfusion, the ratio R_M/R_H returns approximately to control, suggesting a restoration of the control vascular resistance relationship, again confirmed by the representative experiment of Fig. 2. Late in the normovolemic phase hepatic resistance increases again as arterial pressure falls.

Respiration and heart rate typically accelerated during hypotension, from average control values of 60 and 306, to peak values of 80 and 338, respectively (see Table I and Fig. 1).

Effects of transfusion: Normovolemic phase. Mean arterial blood pressure was briefly restored to control, but in about half an hour began a progressive decline. Both portal and inferior vena cava pressure showed transient restoration, then fell with arterial pressure. At 50% time, the arterial, portal and inferior vena cava pressures were 59, 66 and 35%, respectively, of the control values. R_M/R_H was also restored for a brief interval, then decreased slowly during the remainder of the normovolemic phase.

Respiration and heart rate returned toward control following transfusion, but shortly increased to values comparable to those observed during hypotension. Terminally, both slowed drastically, and respiration typically ceased before stoppage of the heart as a terminal event.

Changes in portal flow. The representative experiment (Fig. 2) illustrating flow was selected on the basis of R_M/R_H changes comparable to the animals of series 1, suggesting minimal alteration of splanchnic hemodynamics resulting from introduction of the flow meter in this experiment. It can be noted that changes in arterial, portal and inferior vena cava pressure are comparable to the above series.

Portal flow decreased in approximate proportion to the reduction in arterial pressure, accompanied by very little alteration in R_M, beyond a brief upward spike immediately following bleeding. Nor was there significant change in R_M following transfusion as flow was restored to control. Late in the normovolemic phase, as flow decreased significantly, R_M manifested a slow decrease.

Although quantitatively smaller, R_H showed a significant increase during hypotension. This more than doubled immediately after hemorrhage, and averaged 45% above control during the remainder of the hypotensive period. It was restored to control upon transfusion, but rose to 30% above during the last 30 minutes of the experiment.

Autopsy findings. The serosa and mucosa of both the small and large intestine were usually pale and invariably free of congestion, contrasting markedly to the congested, bloody and fluid filled intestine typically observed in the dog dying of hemorrhagic shock. Little if any free blood was found in the rectum of the monkey.

Discussion. It is of interest to compare the changes in the monkey with those of the dog. The experiments of Wiggers *et al.*(2) done in dogs were similar enough to permit comparison (see Fig. 3). Note the consistently higher values obtained for PVP and IVCP in the dog. Of particular significance is the much greater increase in PVP which follows transfusion. At this time, R_M/R_H is consis-

tently smaller in the dog than in the monkey. The method of vertical analysis suggests that this could result from decrease in R_M, increase in R_H, or combinations of both. Because increase in vascular resistance upon restoration of blood volume appears unlikely, preponderant decrease in R_M can be inferred.

That this is probably the case is demonstrated by a representative experiment selected from a series of dogs in which portal flow was measured with a bristle flow meter (3). Portal flow increased significantly over control in the early post-transfusion phase, at a time when R_M was significantly less than control and R_H had returned to the control average (Fig. 4). Evidently, the elevation of PVP appeared to be the result of relatively greater inflow into the portal vein from the

TABLE I. Hemodynamics of Hemorrhagic Shock in Monkey.* (Average of 6 experiments.)

	Control	Hypotension† % of hypotensive period					Post-transfusion‡ % of post-transfusion period					
		20	40	60	80	95	2½	10	20	40	60	80	100
M.A.B.P., mm Hg 125													
Avg	107	42	41	41	40	41	89	94	88	70	54	42	9
S.D.	18	1.4	1.1	.8	.8	1.9	14.6	16	17.5	28	22	17	6.4
S.E.	7.4	.6	.5	.3	.3	.8	5.9	6.5	7.2	11.3	9	7	2.6
PVP, mm Hg													
Avg	8.6	5.0	5.0	4.8	5.1	5.6	10.0	7.8	7.3	6.2	5.6	5.7	3.7
S.D.	3.3	2.46	2.57	3.0	2.41	2.06	4.0	3.3	2.4	2.7	2.1	2.3	3.0
S.E.	1.35	1.0	1.05	1.2	1.0	.85	1.6	1.3	.9	1.1	.85	.94	1.2
IVCP, mm Hg													
Avg	2.0	.3	.5	.5	.4	.9	2.2	1.8	1.5	.7	.6	.4	.8
S.D.	1.35	1.07	1.53	1.35	1.12	.77	1.84	1.7	1.5	1.26	1.43	1.4	1.8
S.E.	.55	.43	.63	.55	.46	.31	.76	.68	.6	.5	.6	.57	.7
R_M/R_H													
Avg	17.0	9.6	10.0	10.4	8.7	11.0	15.8	18.3	17.5	13.5	11.5	8.4	6.5
S.D.	6.9	4.5	5.4	5.1	3.7	5.2	7.0	7.7	8.0	5.7	4.8	3.5	5.8
S.E.	2.8	1.8	2.2	2.0	1.5	2.1	2.8	3.1	3.2	2.3	2.0	1.4	2.3
R.R.													
Avg	60	69	77	77	79	78	71	72	76	78	77	73	0
S.D.	8.7	11.9	12.2	15.3	18.0	20.3	9	14.9	16.5	15	14	20	—
S.E.	3.5	4.9	5.0	6.2	7.3	8.3	3.7	6.1	7.0	6	6	8	—
H.R.													
Avg	306	317	336	332	331	309	287	303	316	321	317	297	42
S.D.	37	35	43	33	30	21	17	26	17	27	26	58	—
S.E.	15	14	17	14	12	9	7	11	7	11	11	24	—

* Maximum bleeding volumes as % of body wt for Exp. 1-6 were respectively 1.2, 1.4, 2.4, 2.6, 2.1 and 2.2.
† Duration of hypotensive periods was respectively 148, 206, 122, 118, 75 and 117 min.
‡ Duration of post-transfusion periods was respectively 324, 138, 177, 152, 138 and 135 min.

dilated intestinal bed and not to reduced outflow through the hepatic circuit, whose resistance at this time had returned to the control value. Evidence for such increase in intestinal flow of the monkey was not seen in the present series.

Such functional differences may account for the difference in appearance of the intestines at autopsy, for the apparent hyperemia manifested in the canine mesenteric bed would appear to be related to congestion. The reason for difference in behavior of the splanchnic circulation in the dog and monkey cannot now be explained. It is now conceded that splanchnic pooling in the dog is not as significant as was formerly believed (4,5), but it has been suggested that the observed congestive intestinal changes, which involve breakdown of the mucosa and its vasculature, might release toxic substances into the circulation(6). These might be proteolytic breakdown products or metabolites; alternatively, the lesions might permit the escape of substances such as endotoxins and tyramines from the intestinal lumen. In the presence of a liver damaged by anoxia, these substances might more readily invade the systemic circulation, with deleterious consequences(7). Another possibility is that the canine intestinal changes predispose this species to loss of significant amounts of fluid and blood into the bowel, to be irretrievably lost as bloody diarrhea.

If such mechanisms prove important in contributing to the fatal consequence of shock in the dog, it does not appear likely, based on present evidence, that such are applicable to the monkey. Thus, significant differences in the etiology of irreversible shock in the primate and canine appear to be indicated.

Summary. Analysis of pressure gradients in the splanchnic bed of the monkey during a standardized hemorrhagic shock procedure has indicated a preponderant increase in intrahepatic resistance with minimal change in mesenteric (intestinal) resistance during oligemia. Following restoration of the bleeding volume, the control pressure relationship was reestablished. The marked elevation of portal venous pressure, so typical of the dog in this phase of the hemorrhagic shock procedure, was not seen in the monkey. Moreover, the intestine of this species appeared pale and ischemic at autopsy, contrasted to the congested and bloody intestine of the dog. The possible significance of the differences in behavior of splanchnic vasculature in the primate and canine species is considered in the light of the etiology of irreversible shock.

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Susceptibility of a Trachoma Agent Grown in FL Cell Cultures to Antibiotics and a Sulfa Drug.* (27706)

H. BERNKOPF, P. MASHIAH, Y. BECKER (Introduced by N. Grossowicz)
Virus Laboratory, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

In most of the reports of studies on the effect of antibiotics and other drugs on the agent of trachoma, fertilized eggs or laboratory animals have been employed as the host system(1,2,3,4,5,6,7). Recently it has become possible to grow the T'ang strain TE55 of trachoma in cell cultures(8,9,10) and to examine its susceptibility to drugs.

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