Effects of Hemorrhage on Regional Blood Flow Distribution in Dogs and Primates

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ABSTRACT The effects of hemorrhage on arterial
pressure, blood flows, and resistances in the coronary,
mesenteric, renal, and iliac beds of healthy, conscious
dogs and intact, tranquilized baboons were studied. Mild
nonhypotensive hemorrhage (14±2 ml/kg) increased
heart rate and mesenteric and iliac resistances slightly
but significantly, and decreased renal resistance (− 13±
2%). Moderate hypotensive hemorrhage, 26±2 ml/kg,
reduced mean arterial pressure (− 23±2 mm Hg) and
blood flows to the mesenteric (− 56±3%), iliac (− 58±
5%), and coronary (− 39±4%) vascular beds, and in-
creased heart rate (+ 89±9 beats/min) and resistances
in the mesenteric (+ 73±15%), iliac (+ 102±19%),
and coronary (+ 27±5%) beds. In contrast to the
other beds, renal flow rose 11±6% above control and
renal resistance fell 31±2% below control. Renal vaso-
dilatation with hemorrhage was also observed in five
baboons. The increases in mesenteric and iliac resistances
were blocked almost completely by phentolamine, while
the increase in coronary resistance was only partially
blocked by phentolamine. The renal dilatation was not
blocked by phentolamine, propranolol, atropine, or tri-
pelennamine, but was prevented by indomethacin, sug-
gesting that this dilatation was mediated by a prosta-
glandin-like compound.

Thus the peripheral vascular responses to hemorrhage
involve intense vasoconstriction in the mesenteric and
iliac beds. In the normal conscious dog and the intact,
tranquilized primate, the renal bed does not share in
the augmentation of total peripheral resistance with
nonhypotensive and moderate hypotensive hemorrhage,
but does with more severe hemorrhage. In fact, renal

vasodilatation occurs with nonhypotensive or moderate
hypotensive hemorrhage, which can be prevented by
blockade of prostaglandin synthetase with indomethacin.

INTRODUCTION

One of the primary reflex adjustments to hemorrhage in-
volves intense peripheral vasoconstriction (1, 2). The
augmentation of peripheral vascular resistance is
thought to be shared primarily by the renal, mesenteric,
and muscle beds (1, 2). These concepts of reflex circu-
latory responses to hemorrhage have been derived pri-
marily from studies in anesthetized animals or conscious
man and animals utilizing indirect or intermittent tech-
niques for measuring blood flow (1, 2). Since the re-
sponse to hemorrhage is a continuously evolving function,
which cannot be described adequately by one measure-
ment at one or a few instants in time, and since anes-
thesia alters vascular tone in the peripheral beds (3, 4)
and in particular reflex control of the circulation (5, 6),
it appeared important to study instantaneous and continu-
ous responses to hemorrhage in conscious animals in
which all control mechanisms are intact and the com-
plicating influences of anesthesia and acute surgical
manipulation are absent.

Accordingly, the goal of the present investigation was
to clarify the peripheral vascular responses to mild and
moderate hemorrhage in healthy, conscious, trained dogs
and in tranquilized baboons in which arterial pressure
and regional blood flows were measured instantaneously
and continuously. The specific objectives of this study
were to determine (a) the relative roles of the coronary,
mesenteric, renal, and iliac beds in the response to hemor-
rhage, and (b) the efferent mechanisms mediating these
changes.

METHODS

17 normal mongrel dogs (24–34 kg) were studied in the
conscious state. Five baboons (Papio anubis) (24–26 kg),

tranquilized with phencyclidine hydrochloride, 1 mg/kg, were studied. All operations were conducted under i.v. pentobarbital Na, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, Doppler ultrasonic flow transducers were placed around the left circumflex coronary arteries and stimulator electrodes were sutured to the left ventricles (six dogs). Electromagnetic flow transducers[1] were implanted around the ascending aortas in four dogs. Through a midline laparotomy, Doppler ultrasonic (seven dogs) or electromagnetic (one dog) transducers were placed around the mesenteric, left renal, and left iliac arteries. Two of the eight dogs had both Doppler and electromagnetic flow transducers on the renal artery. Five of these eight dogs were studied before and after splenectomy. Doppler ultrasonic flow probes were also placed around the left renal (five baboons), mesenteric (three baboons), and iliac (three baboons) arteries. In all animals a heparin-filled Tygon catheter was implanted in the aorta to sample arterial pressure, while another Tygon catheter was implanted in the jugular vein for phlebotomy. Five additional dogs were anesthetized with pentobarbital Na, 30 mg/kg, and were studied with the abdomen open immediately after placement of the electromagnetic flow transducers[1] on the left renal artery. All animals were maintained on their respective diets before and after the operation.

Arterial pressure was sampled with the previously implanted heparin-filled Tygon catheter and measured with a Statham P23 Db strain gauge manometer. Regional blood flow was measured with an ultrasonic Doppler flowmeter in seven dogs and five baboons. This system, which has been described in detail previously, has a reliable zero reference (7, 8) and in these experiments electrical zero blood flow was determined repeatedly and was confirmed by calibration when the animal was sacrificed. The relationship between velocity, as measured by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. This linear relationship between velocity and volume flow has been demonstrated repeatedly and confirmed by means of timed collections of blood flow (8). At autopsy, it was observed that the vessels were firmly adherent to the flow transducers through a fibrous scar, which minimized changes in the cross-sectional area of the blood vessel within the flow transducers. In six conscious dogs and five anesthetized dogs, an electromagnetic flowmeter[1] was used to measure blood flow. In the experiments in which regional flows were measured, zero flow was determined by inflating a previously implanted hydraulic occlusive cuff, while in the aortic flow experiments, zero flow was assumed to occur during mid and late diastole.

The experiments were conducted 3 wk-2 mo after the operation when the dogs and baboons had recovered from operation and were again vigorous and healthy. Control records of cardiac output, regional blood flows, arterial pressure, and heart rate were obtained continuously while the unsedated dogs were resting quietly in the control state as well as during and after hemorrhage. The experiments were conducted without evidence of the animals' arousal or discomfort. In all animals blood was withdrawn from the catheter in the jugular vein until a sustained fall in mean arterial pressure of 20–30 mm Hg was attained, while in three dogs and three baboons hemorrhage was continued until a sustained fall of over 40 mm Hg occurred. A moderate amount of hemorrhage, i.e., 20–30 mm Hg reduction in mean arterial pressure, was chosen for an

end point because it could be reproduced in all dogs without signs of discomfort or restlessness. The time required to reach this end point averaged 30 min, but ranged from 10 to 60 min. The nonhypotensive hemorrhage was transiently observed during the 10–60-min period required to attain the moderate hypotensive response. The protocol was repeated on separate days after i.v. pharmacologic blockades, i.e., beta adrenergic blockade with propranolol, 1–2 mg/kg, alpha adrenergic blockade with phentolamine, 1.0–2.0 mg/kg, cholinergic blockade with atropine, 0.1–0.3 mg/kg, histaminergic blockade with tripelennamine, 2–4 mg/kg. In five dogs and three baboons the response to hemorrhage was repeated after prostaglandin synthetase blockade with indomethacin, 4–6 mg/kg. In six dogs in which coronary blood flow was measured, values were also recorded during the control period and after hemorrhage with heart rate maintained constant by electrical stimulation at a frequency of 150 beats/min.

The data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph. A cardiotachometer, triggered by the signal from the pressure pulse, provided instantaneous and continuous records of heart rate. Electronic resistor-capacitor filters with 2-s time constants were used to derive mean arterial blood pressure and mean regional blood flows, while a resistor-capacitor filter with an 8-s time constant was used to derive mean aortic flow (cardiac output). Mean regional vascular resistances were calculated as the quotients of mean arterial pressure and regional blood flows, respectively. Mean and late diastolic coronary vascular resistances were calculated as the quotients of mean and late diastolic arterial pressures and coronary blood flows, respectively. Results were compared to pre-hemorrhage control, and changes from control in the different states were compared with the paired t test (9).

RESULTS

While measurements were recorded continuously during hemorrhage, two points were chosen to compare with control values; the first occurred before a reduction in arterial pressure, which occurred after 14±2 ml/kg of hemorrhage and is designated as the mild nonhypotensive hemorrhage response, while the second point was chosen after a sustained 20–30 mm Hg reduction in arterial pressure, which required 26±2 ml/kg of hemorrhage in the normal conscious dogs; this later response was termed the moderate hypotensive hemorrhage response.

Effects of hemorrhage in normal conscious dogs

Systemic effects. Mean arterial pressure in all 17 dogs remained relatively constant at 98±2 mm Hg through the mild hemorrhage response. A sustained decrease in mean arterial pressure, averaging 23±1 mm Hg, occurred at 26±2 ml/kg.

Heart rate increased slightly from 75±3 to 92±4 beats/min ($P < 0.01$) before arterial pressure fell, and then reached a maximum of 164±6 beats/min while mean arterial pressure was falling, and was at 118±5 beats/min during the moderate hemorrhage response, i.e., during the period of sustained hypotension.
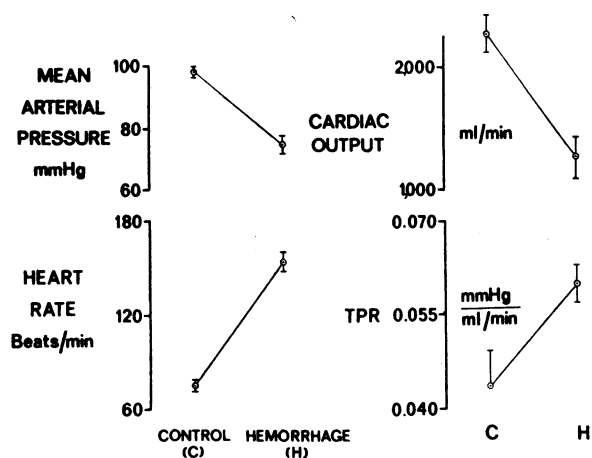
FIGURE 1 Average±SEM maximal effects of moderate hypotensive hemorrhage on mean arterial pressure, heart rate, cardiac output, and total peripheral resistance (TPR).

Cardiac output fell from 2.3±0.2 to 2.1±0.3 liter/min (NS) during the mild nonhypotensive hemorrhage response and then gradually fell to 1.3±0.3 liter/min with moderate hypotensive hemorrhage, while total peripheral resistance rose from a control of 0.044±0.006 to 0.059± 0.004 mm Hg/ml/min at the point of sustained hypotension (Fig. 1).

Coronary bed. Mean left circumflex coronary blood flow rose slightly (+ 17±3%) (P < 0.05) and transiently above a control of 38±3 ml/min during the mild

nonhypotensive hemorrhage response and then fell by 39±4% (P < 0.01) below control during sustained hypotension; at this point, i.e., during the moderate hypotensive response, mean coronary vascular resistance had increased from 2.65±0.14 to 3.38±0.21 mm Hg/ml/min (P < 0.01). When heart rate was maintained constant by electrical stimulation at a frequency of 150 beats/ min during control and sustained hemorrhagic hypotension, during hemorrhage, mean left circumflex coronary flow fell by 47±4% from a control of 49±4 ml/min (P < 0.01) and mean coronary vascular resistance rose from 2.10±0.12 to 3.06±0.19 mm Hg/ml/min (P < 0.01). The changes in late diastolic coronary flow and resistance paralleled the mean values.

Mesenteric and iliac beds (eight dogs). The mesenteric and iliac beds responded similarly to hemorrhage (Fig. 2). Mesenteric and iliac flows fell from control values of 305±16 and 113±6 ml/min to 256±13 and 90±6 ml/min, respectively, during the mild nonhypotensive hemorrhage response, and declined to lower levels during the moderate hypotensive hemorrhage response. At that point, mesenteric flow had decreased by 56±3% to 136±13 ml/min and resistance had increased from 0.33±0.02 to 0.59±0.06 mm Hg/ml/min, while iliac flow had fallen by 58±5% to 46±4 ml/min and iliac resistance had risen from 0.88±0.05 to 1.72±0.11 mm Hg/ml/min. These changes were all significant (P < 0.01) (Fig. 3). When the changes for flow or resistance in the mesenteric and iliac beds were compared
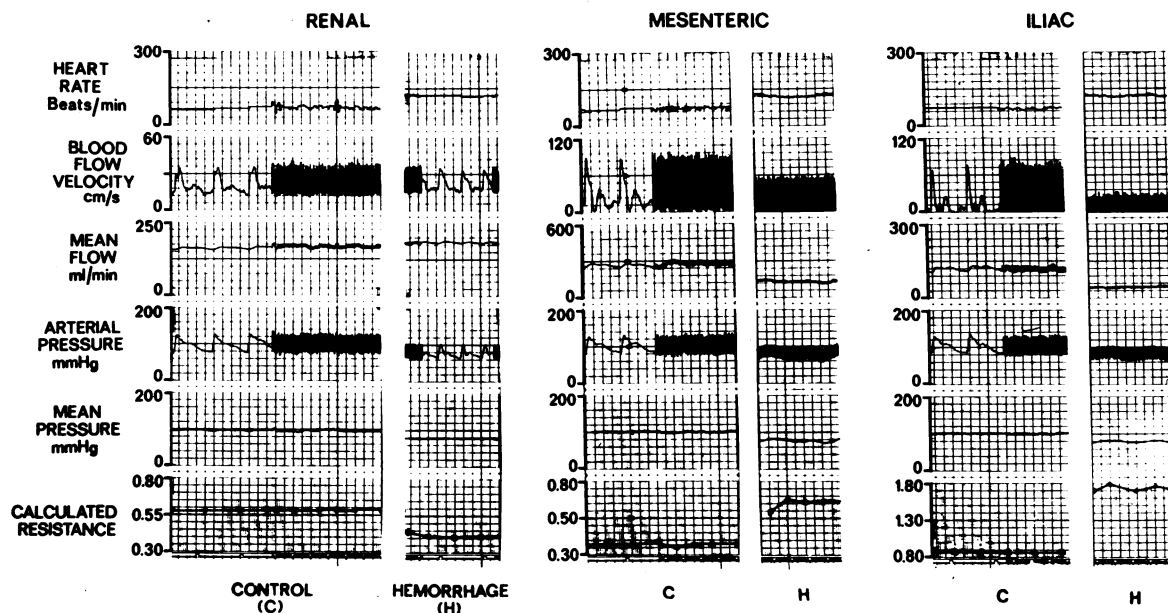

FIGURE 2 Typical responses of renal, mesenteric, and iliac beds to moderate hypotensive hemorrhage, 26 ml/kg. Responses of heart rate, phasic and mean blood flows, arterial pressures, and calculated mean vascular resistances are shown. In the normal conscious dog, intense mesenteric and iliac vasoconstriction occurred, while the renal bed dilated.
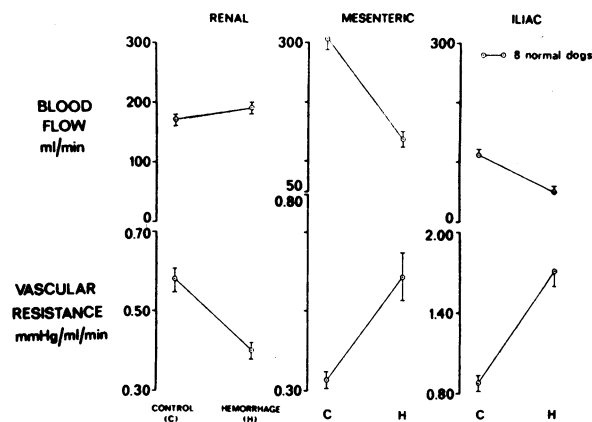
FIGURE 3 Average±SEM values during control and after moderate hypotensive hemorrhage (mean arterial pressure reduction of 20–30 mmHg) of renal, mesenteric, and iliac beds.

as percent change from control, the responses for these beds with moderate hemorrhage were not significantly different.

Five of these dogs were restudied in the conscious state after recovery from splenectomy. A sustained reduction in mean arterial pressure, averaging 24±2 mm Hg, occurred after withdrawal of significantly less ($P <$ 0.01) blood, 17±2 ml/kg, as compared to 26±2 required before splenectomy; the smaller amount of hemorrhage required reflects the reservoir function of the canine spleen. However, once the same degree of hypotension had been achieved, the alterations in resistances in the mesenteric and iliac beds were not different from those before splenectomy.

Renal bed (eight dogs). In contrast to the responses of the mesenteric and iliac beds during the nonhypotensive hemorrhage response, renal blood flow increased 15±4% ($P < 0.05$) above a control of 173±8 ml/min and resistance decreased by 13±2% ($P < 0.05$) from a control of 0.58±0.03 mm Hg/ml/min (Table I). During the moderate hypotensive hemorrhage response renal flow was slightly (11±6%) (NS) above control and renal resistance was at 0.40±0.02 mm Hg/ml/min, which was 31±2% ($P < 0.01$) below control (Fig. 3). At no time during hemorrhage, when arterial pressure was maintained, or with reductions of pressure of 20–30 mm Hg, or during the reinfusion of the shed blood, was renal resistance above control levels. The reductions of calculated renal resistance were observed when renal flow was masured with both the Doppler and electromagnetic flowmeters and regardless of the rate of withdrawal of blood (10 min—1 h).

Five dogs in which renal blood flow was measured were restudied after recovery from splenectomy. As before splenectomy, when arterial pressure fell from 96±4 to 72±4 mm Hg, renal flow did not fall and calculated renal vascular resistance decreased 27±3% from a control of 0.61±0.05 mm Hg/ml/min.

To determine whether renal vasoconstriction would occur with more severe hemorrhage, in three dogs the renal vascular response to severe hemorrhage was examined by continuing withdrawal of blood after the moderate hypotensive hemorrhage response in which the fall in arterial pressure of 20–30 mm Hg had been sustained. When hemorrhage reached 28, 31, and 35 ml/kg, renal dilatation was no longer observed, i.e., renal vascular resistance returned to control levels and mean ar-

TABLE I.
Renal Vascular Effects of Hemorrhage in Dogs and Primates

	Mild nonhypotensive	Moderate hypotensive	Severe hypotensive
Blood loss, ml/kg			
Dog	14±2*	26±2*	50*
Baboon	6±1*	14±2*	27*
Δ Mean arterial pressure, %			
Dog (control = 98±3 mm Hg)	−2±1	−23±2*	−42*
Baboon (control = 103±3 mm Hg)	−2±1	−23±2*	−53*
Δ Renal blood flow, %			
Dog (control = 173±8 ml/min)	+15±4‡	+11±6	−67*
Baboon (control = 150±5 ml/min)	+7±2‡	−1±1	−69*
Δ Renal resistance, %			
Dog (control = 0.58±0.03 mm Hg/ml/min)	−13±2‡	−31±2*	+55*
Baboon (control = 0.68±0.02 mm Hg/ml/min)	−9±2‡	−22±2*	+51*

* Significant change from control, $P < 0.01$.
‡ Significant change from control, $P < 0.05$.

CONTROL   **HEMORRHAGE**

HEART RATE
(beats/min)

300
150
0

RENAL
FLOW
VELOCITY
cm/s

60
30
0

MEAN
RENAL
FLOW
ml/min

350
175
0

ARTERIAL
PRESSURE
mmHg

200
100
0

MEAN
PRESSURE
mmHg

200
100
0

MEAN
RENAL
RESISTANCE
mmHg
─────
ml/min

0.90
0.65
0.40

1 S   30 S   30 S   1 S   30 S

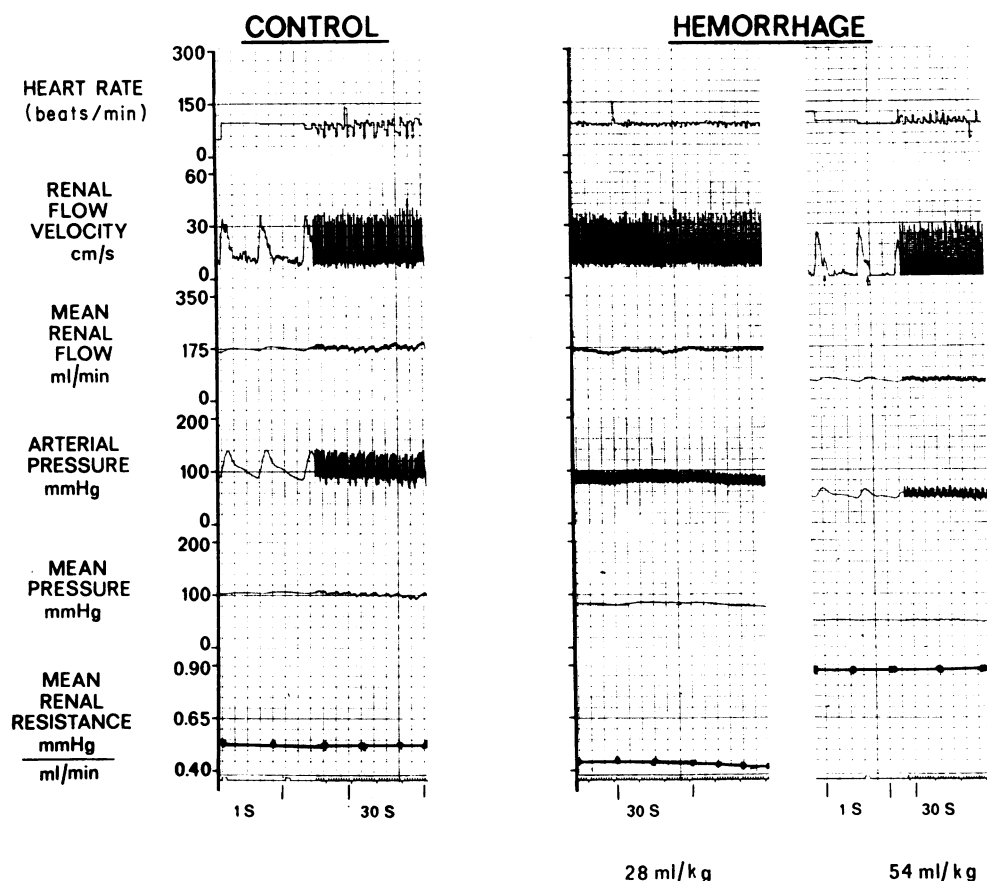28 ml/kg   54 ml/kg

FIGURE 4   Renal responses to moderate hypotensive hemorrhage (middle panel) and severe hemorrhage (right panel) compared to control (left panel) in a conscious dog. Renal dilatation occurred with moderate hemorrhage, while constriction occurred with severe hemorrhage. The arrows on the phasic renal flow tracings during severe hemorrhage point to occurrence of possible reverse renal flow.

terial pressure remained depressed by an average of 25 mm Hg, but renal flow fell by an average of 27% from a prehemorrhage level of 172 ml/min. After 50 ml/kg had been withdrawn, arterial pressure had declined to an average of 58% of control, renal flow fell to 33% of control and renal resistance rose to an average of 55% above control (Fig. 4).

Effects of blocking agents on regional vascular responses to hemorrhage (five dogs)

Alpha receptor blockade. Phentolamine, 1 mg/kg, increased heart rate from 73 ± 5 to 111 ± 9 beats/min and decreased mean arterial pressure (from 101 ± 4 to 90 ± 4 mm Hg), and mesenteric $(-17\pm3\%)$, iliac $(-15\pm3\%)$, renal $(-12\pm2\%)$, and coronary $(-11\pm2\%)$ vascular resistances. All of these changes were significant $(P < 0.05)$. Only 14 ± 2 ml/kg hemorrhage was required to produce a sustained 20–30 mm Hg reduction in mean arterial pressure, indicating that the ability of the circulation to withstand hemorrhage was significantly im-

paired. At the moderate hypotensive response, the increases in mesenteric $(+22\pm5\%)$ and iliac $(+17\pm4\%)$ resistances were significantly less than without blockade $(P < 0.01)$. The elevation in coronary vascular resistance with hemorrhage at a constant heart rate $(\pm0.65\pm0.10$ mm Hg/ml/min) was less after alpha blockade than in the control state $(+0.96\pm0.10$ mm Hg/ml/min) $(P < 0.05)$. However, the reduction in renal resistance $(-29\pm3\%)$ was similar (Table II).

Thus, alpha receptor blockade attenuated the hemorrhage-induced increases in mesenteric and iliac resistances substantially, and coronary resistance slightly, but did not affect the renal vasodilatation.

Other blockades. Beta receptor blockade with propranolol (1–2 mg/kg), cholinergic blockade with atropine (0.1–0.3 mg/kg), and histaminergic blockade with tripelennamine (1–2 mg/kg), did not affect the pattern of differential vasoconstriction observed with hemorrhage at the point of sustained hypotension. After each of these blockades, the increases in mesenteric and iliac resis-

TABLE II

Effects of Blockades on Renal Response to Hemorrhage in Conscious Dogs

	Control ±SEM	Response ±SEM	Δ Control ±SEM
Mean arterial pressure, *mm Hg*			
Without blockade	98±3	75±3	−23±2*
Alpha adrenergic blockade	90±2	68±3	−22±2*
Beta adrenergic blockade	96±2	75±3	−21±2*
Cholinergic blockade	99±2	77±2	−22±2*
Histaminergic blockade	115±5‖	90±3	−25±3*
Prostaglandin blockade	98±3	77±3	−22±2*
Mean renal blood flow, *ml/min*			
Without blockade	173±8	191±11	+18±10
Alpha adrenergic blockade	180±9	193±10	+13±7
Beta adrenergic blockade	167±10	169±15	+2±6
Cholinergic blockade	174±12	178±13	+4±7
Histaminergic blockade	177±8	184±9	+7±6
Prostaglandin blockade	168±12	92±14	−76±5*§
Calculated mean renal resistance, *mm Hg/ml/min*			
Without blockade	0.58±0.03	0.40±0.02	−0.18±0.02*
Alpha adrenergic blockade	0.51±0.03¶	0.36±0.02	−0.15±0.02*
Beta adrenergic blockade	0.59±0.04	0.46±0.04	−0.13±0.02*
Cholinergic blockade	0.58±0.04	0.44±0.03	−0.14±0.02*
Histaminergic blockade	0.66±0.04¶	0.49±0.04	−0.17±0.04*
Prostaglandin blockade	0.60±0.04	0.90±0.12	+0.30±0.08*§

* Significant change from control $P < 0.01$.
‡ Significant change from control $P < 0.05$.
§ Significantly different from response without blockade $P < 0.01$.
‖ Significantly different from control value without blockade $P < 0.01$.
¶ Significantly different from control value without blockade $P < 0.05$.

tances and reduction in renal resistance with hemorrhage were not significantly different from the responses without blockade (Table II).

Prostaglandin synthetase blockade (five dogs). Indomethacin, 4–6 mg/kg, caused little change in arterial pressure, indicating that indomethacin did not affect significantly the ability of the circulation to withstand hemorrhage. The increases in heart rate, iliac and mesenteric vascular resistance that occurred as a consequence of hemorrhage were not significantly different from those occurring without indomethacin. However, the response of the renal vascular bed was considerably different. Renal flow not only failed to rise with nonhypotensive hemorrhage, but actually fell slightly (− 16±3%) ($P < 0.05$); renal vascular resistance rose at this time ($P < 0.05$). During the period of moderate hypotensive hemorrhage, renal blood flow fell by 45±5% ($P < 0.01$) from a control of 168±12 ml/min, while renal resistance increased by 49±5% ($P < 0.01$) from a control of 0.60± 0.04 mm Hg/ml/min (Fig. 5). Thus, indomethacin altered the normal renal response to hemorrhage by reversing the dilatation to sustained constriction.

Combination of blocking agents (three dogs). When blood was withdrawn to reduce mean arterial pressure by 20–30 mm Hg after combined alpha and beta receptor, cholinergic and histaminergic blockades renal flow remained essentially at control levels and renal vasodilation occurred with hemorrhage.

Renal vascular response to hemorrhage in primates

Hemorrhage was induced in five baboons tranquilized with phencyclidine hydrochloride, 1 mg/kg. The mild nonhypotensive hemorrhage response occurred after 6±1 ml/kg of blood was withdrawn, while 14±2 ml/kg of hemorrhage was required to decrease mean arterial pressure by 23±2% from a control value of 103±3 mm Hg (Table I). Heart rate rose from 95±9 to a maximum of 162±13 beats/min just before the moderate hypotensive response. In the three baboons in which mesenteric and iliac blood flows were measured, mild nonhypotensive hemorrhage reduced these flows and increased resistance in these beds by amounts comparable to those in the dogs with nonhypotensive hemorrhage. With moderate hypo-

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tensive hemorrhage, mesenteric and iliac blood flows fell by averages of 46 and 40%, respectively, while resistances in these beds rose by averages of 43 and 35%, respectively.

Renal blood flow rose by 7±2% ($P < 0.05$) from a control of 150±5 ml/min during the mild nonhypotensive hemorrhage response, while renal resistance fell by 9±2% ($P < 0.01$) from a control of 0.68±0.02 mm Hg/ml/min (Table I). During the moderate hypotensive response, renal flow was not significantly different from control, but renal resistance had declined by 22±2% (Table I). With further hemorrhage averaging 27 ml/kg carried out in three baboons, renal flow fell by an average of 69% and renal resistance rose by an average of 51%.

After indomethacin, 4–6 mg/kg, in three baboons, mild nonhypotensive hemorrhage failed to elicit a reduction in renal resistance. During the moderate hypotensive hemorrhage response, when mean arterial pressure had fallen from 108 to 84 mm Hg, renal flow fell by 43% and resistance rose by an average of 38%.

Thus, the peripheral vascular response in the tranquilized baboon was like that in the conscious dog. Renal vasodilation, which could be prevented with indomethacin, occurred in both species.

Effects of anesthesia and laparotomy on renal response to hemorrhage (five dogs)

Pentobarbital, Na, 30 mg/kg, followed by surgical implantation of the flow transducer, markedly impaired the ability of the circulation to withstand hemorrhage: only 9±2 ml/kg of hemorrhage was necessary to cause a sustained decrease in arterial pressure of 20–30 mm Hg from a control value of 102±4 mm Hg. At this point renal flow had decreased by 10±2% ($P < 0.05$) from a control of 169±10 ml/min, and renal resistance was 8±2% ($P < 0.05$) below a control level of 0.61±0.04 mm Hg/ml/min. However, when hemorrhage was continued to 26 ml/kg, renal flow had fallen to 56±4 ml/min, arterial pressure had fallen to 52±4 mm Hg, and renal resistance had risen ($P < 0.01$) to 0.94±0.08 mm Hg/ml/min.

Thus the response to hemorrhage was affected by anesthesia and laparotomy as follows: much less blood loss was required to effect a 20–30 mm Hg decrease in arterial pressure. At that point, a minor degree of renal dilatation ($P < 0.05$) was observed, but when the amount of hemorrhage was similar to that in conscious dogs, intense renal vasoconstriction was observed.

DISCUSSION

Arterial pressure is maintained during hemorrhage to a large extent through peripheral vasoconstriction (1, 2) induced by increased sympathetic vasoconstrictor tone (1, 2), catecholamine secretion (10, 11), and renin
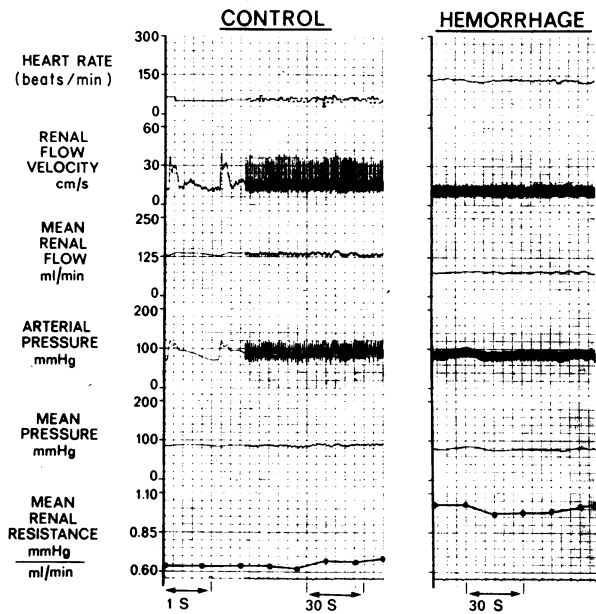

FIGURE 5 Typical renal response to moderate hypotensive hemorrhage, 25 ml/kg, after pretreatment with indomethacin, 4 mg/kg. This is the response for the same dog as shown without blockade in Fig. 1. Instead of renal dilatation, marked constriction occurred.

release (10, 12). The augmentation of total peripheral resistance has been thought to involve the renal, mesenteric, and limb beds (1, 2). In the present study, hemorrhage increased total peripheral resistance as expected, but the extent to which the various regional beds participated in this increase in total resistance was variable. Intense reductions of blood flows and increases in resistances occurred in the coronary, mesenteric, and iliac beds; blood flow to the mesenteric and iliac beds fell even with mild hemorrhage, while arterial pressure was still maintained and fell substantially further with moderate hemorrhage. While the mesenteric and iliac vasoconstriction was most likely due predominantly to alpha adrenergic vasoconstriction, the results of the present study suggest that coronary vasoconstriction may have been due to another mechanism, e.g., reduced myocardial oxygen demands, since the coronary resistance also increased with hemorrhage after alpha adrenergic blockade with phentolamine. While some alpha adrenergic coronary vasoconstriction with hemorrhage was apparent in the present study, it appears to play a minor role. Prior studies in anesthetized animals have found coronary vasodilatation predominant with hemorrhage (13–16), while one investigation in conscious animals, by Granata, Huvos, Pasque, and Gregg found vasoconstriction predominant, as in the present study (17). These investigators suggested that the increase in coronary resistance was probably a consequence of vasoconstriction mediated by the sympathetic nervous system.

In contrast to the striking vasoconstrictor responses of the mesenteric and iliac beds, renal flow was well maintained and renal resistance fell with both mild and moderate hemorrhage. Often renal flow rose before pressure fell and renal dilatation persisted even when pressure had declined by 23±2 mm Hg. In the baboons as in the dogs, renal dilatation occurred with hemorrhage both before a reduction in arterial pressure and also after a 20–30 mm Hg fall in arterial pressure. Thus renal vasodilation occurred in both species. The major difference was the amount of hemorrhage tolerated before arterial pressure fell and required to produce a sustained reduction in arterial pressure, i.e., 14±2 ml/kg in the baboons and 26±2 ml/kg for the dogs. In contrast, the concept that the renal bed responds to hemorrhage with constriction is widely accepted (1, 2, 18–27). In fact, there are several studies which indicate the renal bed has the most intense constriction of all peripheral beds studied (25, 26).

There are several possible explanations for the discrepancy between the conclusion of previous investigations, indicating intense renal vasoconstriction with hemorrhage (18–27), and those in the present one, demonstrating sparing of the renal bed. Three important features of the present investigation were (a) renal blood flow was measured in the conscious animal, (b) these measurements were instantaneous and continuous, and (c) hemorrhage was not severe or prolonged, i.e., hemorrhagic shock did not develop. Studies indicating intense renal vasoconstriction with hemorrhage were generally conducted in animals after general anesthesia and surgical manipulation of the kidney (19, 20, 22, 26, 27) or in man and experimental animals utilizing intermittent techniques to measure blood flow (18, 23, 25). Since the renal response to hemorrhage was found to be qualitatively different with the severity of hemorrhage, it is important to note that prior studies utilizing intermittent techniques generally did not measure renal blood flow before pressure fell or when pressure was reduced only 20–30 mm Hg, where dilatation was found in the present study. Moreover, in many studies hemorrhage was more intense than in the present investigation.

On the one hand, anesthesia and recent surgical trauma alter regional blood flow distribution (3, 4) and reflex control of the circulation (5, 6). Thus, it was not surprising that a similar degree of arterial hypotension occurred after 9±2 ml/kg hemorrhage in the anesthetized animals, as compared to 26±2 ml/kg in the conscious animals, indicating that anesthesia impairs circulatory control mechanisms responsible for maintaining pressure in hemorrhage (28). When hemorrhage was continued in the anesthetized animals to 26 ml/kg, renal flow had fallen and renal resistance had risen substantially. This effect has been observed by others with equivalent levels of hemorrhage in anesthetized animals

(19, 20, 22, 24–27). In contrast, in the present study renal dilatation occurred uniformly in the normal conscious animals with similar degrees of hemorrhage. Renal dilatation can be observed in illustrations from previous studies measuring renal flow in response to hemorrhage in conscious animals; in the study by Gregg (29), during moderate hemorrhage when arterial pressure fell substantially, renal flow fell only slightly, indicating that a reduction in renal resistance had occurred, while in the study by Rushmer, Van Citters, and Franklin (30), illustrations showing a decrease in pressure but not renal flow with hemorrhage can also be observed. Thus in the conscious dog mild to moderate hemorrhage induced renal vasodilatation. This same mechanism is present in the anesthetized dogs, but appeared only during mild hemorrhage, less than 10 ml/kg. Selkurt and Elpers also noted that renal flow was well maintained during mild hemorrhage in anesthetized dogs (27). Moreover, Kaihara, Rutherford, Schwentker, and Wagner observed an initial preservation of the renal bed with hemorrhage (31). Similarly, the investigation by Rector, Stein, Bay, Osgood, and Ferris indicated that little change occurred in total renal resistance with hemorrhage and that redistribution of renal blood flow occurred, with vasodilatation actually occurring in the inner cortex (32).

There are also difficulties with the use of intermittent methods of measuring renal blood flow during hemorrhage. For instance, the para-aminohippurate (PAH)[a] method of measuring renal flow during hemorrhage has been demonstrated to be inaccurate when compared with directly measured renal flow (27, 33–37); when compared with an electromagnetic flowmeter, the PAH method indicated an average of 30% lower flow during hemorrhagic hypotension (37). This discrepancy may be due to an accumulation of PAH in the kidney during hemorrhage and hyoptension, which may lead to underestimated renal blood flow measurements utilizing the PAH method (27) or because a redistribution of renal blood flow occurs within the kidney during hemorrhage (24, 32, 38–40). Another difficulty with intermittent techniques, such as the PAH method or the microsphere method, is that intermediate responses will not be observed. For instance, the study by Forsyth, Hoffbrand, and Melmon did not note a fall in renal blood flow with 10% hemorrhage where mean arterial pressure did not fall (23). Moreover, with 30% hemorrhage, when mean arterial pressure had already fallen by 40 mm Hg, a significant increase in renal resistance was not noted. It is possible that if an intermediate point had been studied, renal vasodilatation might have been observed.

Other reasons for the difference between the results of the present and of previous studies include the time of measurement, the severity of hemorrhage, and the presence of circulatory shock. If the hemorrhage is severe, prolonged, or results in shock, it is likely that renal vasoconstriction occurs, as was shown in the present study. In contrast, with relatively brief, mild, or moderate hemorrhage, leading to only a 20–30 mm Hg reduction in arterial pressure, renal dilatation occurs. This concept is in accord with that of Folkow (41), suggesting that the neuron pool supplying the renal vessels has a higher threshold than those supplying muscle and gut. Thus, early vasoconstrictor responses to hemorrhage would occur in muscle and gut with relative sparing of the kidneys, as was actually observed in the present study.

Several sources of error were considered in the present study as well. It was possible that the Doppler flowmeter, which measures velocity, might falsely record an increase in velocity if vessel walls collapsed within the probe. However, it was observed that renal resistance generally declined even before arterial pressure fell, and during the renal dilatation identical techniques showed intense constriction in the systemic, mesenteric, and iliac beds. Furthermore, similar results were obtained with the electromagnetic flowmeter. Moreover, in the anesthetized dogs in this study and the conscious dogs after indomethacin pretreatment (Fig. 5), renal resistance did rise with moderate hemorrhage. Finally, when hemorrhage was continued after the sustained fall of 20–30 mm Hg in the conscious dogs, renal dilatation was no longer observed; in the presence of severe hemorrhage (50 ml/kg), intense renal vasoconstriction was observed (Fig. 4). It was also considered that the canine spleen offers an unusual reserve mechanism, and accordingly studies were performed both before and after splenectomy. Similar results occurred in both cases, although less hemorrhage was required to reduce pressure to the same extent after splenectomy. Similarly, the baboons did not tolerate hemorrhage as well as the conscious dogs, which may be in part due to the absence of the splenic reservoir mechanism and also may be due to the presence of the dissociative agent, phencyclidine, which may disrupt circulatory control mechanisms as in general anesthesia.

The mechanism of the renal vasodilatation did not appear to be mediated by adrenergic, cholinergic, or histaminergic mechanisms, since after pretreatment with these blocking agents, singly or in combination, the renal bed still responded to hemorrhage with dilatation. However, after indomethacin, 4–6 mg/kg, a compound known to inhibit the synthesis of prostaglandin (42), the opposite response to hemorrhage resulted; i.e., substantial renal vasoconstriction occurred. This suggests that a prostaglandin-like compound is responsible for the renal dilatation with hemorrhage. In support of this concept, prostaglandins have been found in the kidney (43) and are thought to play a role in the regulation of renal vascular resistance (44). It has recently been shown that release of prostaglandin could in part be responsible for renal autoregulation (45). Thus, with arterial hypotension, prostaglandin release within the kidney could act to dilate the renal bed, thereby preserving renal flow at low pressures (45).

The relative sparing of the renal bed with low output and low pressure states, as suggested by Folkow (41) has also been observed in previous studies in conscious animals in our laboratory. When heart rate is drastically reduced abruptly in dogs with complete heart block, causing arterial pressure and cardiac output to fall, renal dilation occurs (46). When cardiac output is chronically reduced, as in congestive heart failure, intense mesenteric and iliac but not renal vasoconstriction occurs (47). Thus, the renal vascular bed responds to a variety of low output and low pressure states with less constriction and even dilatation, as in this case with acute hemorrhage.

The volume of hemorrhage required to produce a sustained 20–30 mm Hg reduction in mean arterial pressure might be useful as an index of the circulation's ability to withstand hemorrhage. By this criterion, it is apparent that the intact normal conscious animal was best equipped to withstand hemorrhage and that blockade of cholinergic, beta adrenergic, and histaminergic receptors as well as of prostaglandin synthetase did not impair circulatory control substantially. On the other hand, splenectomy and, to a greater extent, alpha receptor blockade had greater effects in modifying the normal dog's capability to withstand hemorrhage. Hemorrhage was tolerated least well after anesthesia and laparotomy; an equivalent reduction in arterial pressure occurred in the anesthetized dogs with approximately one-third the amount of hemorrhage required in the conscious dogs.

In conclusion, in conscious dogs with all control mechanisms intact, the peripheral vascular adjustments to relatively rapid and moderate hemorrhage include modest constriction in the coronary bed and intense mesenteric and iliac vasoconstriction while the renal bed dilates. Renal dilatation after less severe hemorrhage also occurs in the intact, tranquilized primate. The renal dilatation, which can be classified as an autoregulatory response, appears to be due to prostaglandin release. With more severe hemorrhage, constriction occurs in the renal bed as well and can overcome the autoregulatory response.

ACKNOWLEDGMENTS

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