Differential Response of Renal and Femoral Blood Flows and Vascular Resistances

Hypotensive and Hypertensive Procedures

By John C. McGiff, M.D., and Domingo M. Aviado, M.D.

According to existing information, the coronary and cerebral vascular beds are regulated largely by nonnervous (humoral, metabolic, and mechanical) influences, whereas the renal, splanchnic, and limb vascular beds are regulated in varying degrees by nervous influences. In the latter group of vascular beds it is not possible to specify the extent of nervous control. This uncertainty is based considerably upon the paucity of data derived from simultaneous determinations of two or more regional flows. When such studies have been made, comparing simultaneous regional flows of the kidney and extremity, the conclusions regarding reactivity of these beds have been opposite. On the one hand, Sapirstein et al.1 found in rats that hemorrhage caused a greater increase in vascular resistance of the kidney than of the extremity. Similarly, Assali and Westersten2 found in dogs and sheep that the renal bed was more sensitive to angiotensin and levarterenol than that of the extremity.

On the other hand, the extremities have been reported to be more reactive than the kidney to occlusion of the common carotids in the dog,3 to bulbar stimulation in the cat,4 to the application of heat to a contralateral extremity or the intravenous injection of hypotensive drugs in man.5,6 The opposite conclusions are quite likely related to the differences in stimuli, species, and techniques for measuring blood flow.

This study was designed to characterize further two vascular beds in their response to direct nervous (increased intracranial pressure), reflex nervous (5 per cent oxygen, bilateral carotid occlusion), humoral (isoproterenol, angiotensin, levarterenol), and hypovolemic (bleeding and aortic constriction) stimuli. The experiments reported below deal exclusively with one species (anesthetized dog) in which renal and femoral blood flows are measured by one technique (venous outflow recorder).

Methods

Nineteen mongrel dogs weighing 15 to 26 Kg. were anesthetized with morphine sulfate (2 mg./Kg., S.C.) and chloralose (70 mg./Kg., I.V.). The trachea was cannulated and the lungs were ventilated by a Starling Ideal pump. Mannuronate (10 mg./Kg.) or heparin (200 to 400 international units/Kg.) was administered intravenously as the anticoagulant. A Sanborn polyviso recorded three or all four of the following: (1) mean arterial blood pressure by a Statham transducer from a catheter inserted via either the left femoral or carotid artery; with constriction of the abdominal aorta, the aortic pressure was recorded simultaneously above and below the point of constriction; (2) central venous pressure by a Statham transducer from a catheter inserted via the left femoral vein; (3) mean femoral or iliac venous outflow; and (4) mean renal venous outflow. In measuring such venous outflows, the vein was cannulated and connected to a closed collapsible reservoir depicted in figure 1. The degree of collapse of this reservoir was adjusted during the control period and maintained during application of the stimulus. This was designed to keep constant the venous pressure of the regional beds under study. This reservoir was used to collect the venous outflow, but was continually emptied by means of a manually controlled sigmamotor pump which returned the blood to the femoral or jugular vein of the animal. A Shipley-Wilson rotameter was inserted between the pump and the dog to measure and...
register venous outflow. The reservoir was continually checked visually to assure that the pump emptied it in spite of induced increases in venous outflow.

The following procedures were applied: (a) temporary constriction of the abdominal aorta immediately above the origin of the renal arteries by means of a ligature inserted via the same flank incision used for exposing the renal vein; (b) administration of a gas mixture of 5 per cent oxygen in nitrogen via the Starling pump; (c) bleeding via a cannula in the femoral artery (opposite to the side in which flow was measured) amounting to 8 to 10 ml./Kg. for a period up to four minutes; (d) increasing the intracranial pressure by trephining the parietal bone, inserting a metal cannula (1 cm. in diameter) and attaching it to a bottle of saline. Pressure was increased by temporarily exposing the saline to compressed air, while measuring the pressure by means of a mercury manometer; (e) intravenous injection of each of the following: angiotensin (Hypertensin, Ciba) 0.1 to 2 μg./Kg., levarterenol 1.0 to 20 μg./Kg., isoproterenol 1 to 10 μg./Kg., and bretylium 2.5 to 5 mg./Kg.

**Results**

**Control Blood Flows**

An important feature of the experiments is that blood flows in both the renal and femoral veins were measured by an identical method. The venous drainage of these regions differs. The femoral bed has important collaterals, whereas the kidney has only a single efflux (the renal vein). The assumption has been made that the flow in the femoral vein is an index of total femoral venous flow. The pressure in the femoral vein is kept constant, thereby negating resistance changes induced by the recording system (cannula, tubing, flowmeter). Thus shunting of blood from the area of femoral vein drainage to collateral channels is reduced or eliminated, since the perfusion pressure is the same for each. Shunting in the opposite direction, i.e., collaterals to the area of femoral vein drainage, is held to be minor. The control values in a group of 20 dogs were as follows: renal venous blood flow, mean 151 ml./min. (range 82 to 246); femoral venous blood flow, mean 42 ml./min. (range 18 to 92); one iliac blood flow (168 ml./min.); and aortic blood pressure, mean 116 mm. Hg (range 70 to 145). The general plan was to apply one experimental stimulus and to express the results as the maximal percentage change in venous outflow. Since venous pressure was kept constant, the vascular resistance of either the kidney or the hindlimb was calculated by dividing aortic blood pressure by the corresponding venous outflow, and the percentage change in vascular resistance was calculated and compared with that for the percentage change in blood pressure. Two or more procedures or drugs were repeatedly applied to each dog. The sequence of drugs and procedures was altered in each case to minimize prolonged influence of a previous procedure or cross-tachyphylaxis in the case of drugs. The interval between two procedures was at least three minutes, or longer if the control parameters were unsteady.

Before the individual results are described, it is important to list the possible patterns of changes in the five measurements: blood pressure, renal blood flow, renal vascular resistance, femoral blood flow, and femoral vascular resistance.

**Pattern A.** The fall in blood pressure is accompanied by proportional reductions in

---

Image: Scheme of simultaneous regional flow measurements; rotameter (R); sigmamotor pump (P).
blood flows; renal and femoral vascular resistance are therefore unchanged. This simple pattern of unchanged vascular resistances signifies that the net effect of the particular stimulus is unaltered vascular resistance; the reduction in blood flow is exclusively the outcome of a fall in blood pressure. (This pattern was never encountered following any hypotensive or hypertensive procedure.)

Pattern B. The rise in blood pressure is accompanied by either a smaller increase in flow or even a decreased flow; thus vascular resistance is increased. (This pattern was encountered following most hypertensive procedures.)

Pattern C. The rise in blood pressure is accompanied by an increase in flow, but the blood flow is increased by a larger percentage; vascular resistance is therefore reduced. (This pattern was encountered as a transient initial effect following some hypertensive drugs.)

Pattern D. Fall in blood pressure, but the blood flow is reduced by a greater percentage; vascular resistance is therefore increased. (This pattern is exemplified in the following hypotensive procedures: bleeding and, occasionally, administration of isoproterenol.)

Pattern E. Fall in blood pressure, but the blood flow is either reduced by a smaller percentage, unchanged, or is even increased; thus vascular resistance is reduced. (This pattern is exemplified in the next paragraph.)

Aortic Constriction

Partial constriction of the aorta above the renal arteries was performed to reduce directly the blood pressure in the descending aorta. It permits comparing the degree of the reductions in blood flows for the renal and femoral vascular beds. A typical response is depicted in figure 2, in which the ligation of the abdominal aorta caused the expected fall in aortic blood pressure below the constriction, and a fall in blood flow of the renal and femoral veins. The reduction in renal

Figure 2
Aortic constriction (AC). Note the lag in the reduction of femoral flow and the immediate reduction of renal flow following aortic constriction.

Circulation Research, Volume IX, November 1941
Figure 3
Summary of results of hypotensive procedures; mean aortic blood pressure (BP); renal flow (RF); renal vascular resistance (RVR); femoral flow (FF); femoral vascular resistance (FVR); aortic constriction (AORTIC CONSTR.). Percentile change of control values in mean blood pressure, flows, and resistances to hypotensive procedure. The individual values are represented by points (*, intact; o, after bretylium). The bars represent the average of the values.

Blood flow occurred promptly after partial occlusion but the femoral flow lagged, presumably due to the larger blood volume contained in the capacitance vessels of the femoral bed. The constriction of these vessels (venules, veins) would contribute to venous outflow after arterial constriction. The percentage reductions in flows are less than that of the fall in blood pressure, so that the vascular resistances were reduced (summary of five dogs in fig. 3). In each of the five dogs, the percent reduction in renal blood flow is larger than that of the femoral flow, and the decrease in femoral vascular resistance is larger than decrease in the renal.

The observed reduction in vascular resistance of both beds following a reduction in aortic blood pressure can possibly be due to a nervous factor and/or a nonnervous response. The former is very possible because the ligation is accompanied by a rise in pressure proximal to the point of ligation. This would cause excitation of the aortic and carotid sinus baroreceptors and reflex vasodilation. Bretylium was administered in one dog to block sympathetic vasoconstrictor fibers. The results are essentially similar to those with intact innervation (fig. 3). As in the normal dogs, the vascular resistance of the extremities showed a greater fall than the renal.

Hemorrhage
Four dogs were bled by 8 to 10 ml/Kg. in a period of two to five minutes, and the effects were similar to aortic occlusion in the following respects: reduction in aortic blood pressure, renal blood flow, femoral blood flow, and femoral vascular resistance (figs. 3 and 4). The only difference is that following hemorrhage, there was an increase in renal vascular resistance. The reasons for the difference in behavior of renal vascular resistance in hemorrhage compared to aortic occlusion were not explored. One possibility is that constriction of renal vessels in the former emphasizes the greater sensitivity of these vessels to vasoconstrictor stimuli, both neurogenic and humoral, and subsequent experiments support this possibility.

Isoproterenol
Reductions in blood pressure, renal vascular resistance, and femoral flow were consistently produced by this agent administered intravenously (fig. 3). Renal flow and femoral resistance changes were variable. The latter effect is seemingly contrary to the known vasodilating properties of isoproterenol, but is consistent with baroreceptor-induced vasoconstrictor activity overshadowing the local effects of the drug. An increase in femoral blood flow was encountered when the injection of isoproterenol was repeated after bretylium, presumably due to abolition of reflex nervous activity elicited by the hypotensive effect of isoproterenol.

Increased Intracranial Pressure
The excitation of the autonomic nervous system was induced by increasing the intracranial pressure. The expected rise in aortic blood pressure was accompanied by a reduction in both renal and femoral blood flows, but the reduction in the former was more severe than in the latter (fig. 5). This dif-
ference was reflected by a consistent increase in renal vascular resistance, but either a rise (six dogs) or a fall (two dogs) in femoral vascular resistance. The increase in vascular resistance of both beds is the most intense of the procedures which caused vasoconstriction (fig. 6).

After chemical sympathectomy (bretylium), what had been a striking renal constrictor response was reduced during increased intracranial pressure. Renal flows always increased, exceeding control flows in two of three experiments in which bretylium was employed. Renal resistance, though reduced, remained above control values. However, renal resistance characteristically increased with an increase in perfusion pressure even in the denervated state. An alternate or supplementary explanation for this maintained increase in renal resistance following bretylium is an increased amount of humoral pressor substances during increased intracranial pressure, the activity of which is uninfluenced by bretylium. Femoral flow following bretylium increased strikingly, always exceeding control values; femoral resistance consistently fell below control values.

Levarterenol

The effects of this catecholamine are divided into those registered by doses of 5 μg./Kg. or less, and those of doses larger than 5 μg./Kg. The effects of small doses were similar to those of increased intracranial pressure: rise in aortic blood pressure, reduced renal blood flow, and increased renal vascular resistance (fig. 6). The only difference from the neurogenic form of hypertension is that levarterenol caused a biphasic action in femoral blood flow, an initial rise in flow followed by a reduction, and corresponding changes in resistance in the opposite direction (fig. 7). The biphasic response in flow and resistance during a simple rise in blood pressure suggests at least two definite mechanisms initiated by levarterenol: rise in pressure will increase flow, and vasoconstriction will reduce flow. Both factors should be expected to operate in the femoral bed, but the former is overshadowed by the latter; the renal vessels are, therefore, more sensitive to the local vasoconstrictor action of levarterenol than femoral vessels.

The larger doses of levarterenol caused effects which were qualitatively similar to those induced by the smaller doses, but were more intense. The mean increase in renal vascular resistance approximates that induced by increased intracranial pressure.

Angiotensin

The pattern of response is similar to that of levarterenol: increased blood pressure, consistent increase in renal vascular resistance and biphasic effect on femoral vascular resistance (fig. 6). The increase in sensitivity of the renal vessels is again demonstrated for this humoral agent.

Anoxia

The inhalation of 5 per cent oxygen and common carotid occlusion are rather unique among the hypertensive procedures because they affect the femoral vessels more than the renal (fig. 6). There is a rise in pressure and in vascular resistance in both beds, but the rise in the femoral bed is greater than in the renal. This observation does not necessarily negate the generalization that renal vessels are more sensitive to vasoconstrictor impulses. Anoxia excites both vasoconstriction via
Increase in intracranial pressure causes reduction in blood flows. The prompt recovery of the femoral flow and the delay of the renal flow in returning to control after cessation of increased intracranial pressure are noted.

Chemoreceptors and vasodilatation by a local action, so that it is possible that reflex vasoconstriction may be more intense for the renal bed, which is counteracted by a local vasodilatation even more intense than that induced in the femoral vessels. This possibility was not explored. That the renal bed is less sensitive than the femoral bed to reflex-induced vasoconstrictor activity is supported by the observation that follows.

Common Carotid Occlusion

The increase in femoral resistance is greater than renal resistance, presumably due to a reduction in baroreceptor activity (fig. 6).

Skinning the leg (2 experiments) did not significantly alter the response to any of the stimuli. This was done to support the assumption that the femoral bed responses were primarily those of skeletal muscle. The cutaneous bed was held to be a component of femoral flow which was not a determinant of the pattern or type of femoral bed response to a stimulus.

Discussion

These experiments serve to define reactivity of the femoral and renal vascular beds to a variety of stimuli. The factors which affect blood flow and vascular resistance will now be discussed.

Relationship of Blood Pressure to Blood Flow

A reduction in regional flow was registered with most hypertensive procedures. The greatest reduction in both regional flows was produced by the intravenous injection of levarterenol. The most potent pressor stimulus, increased intracranial pressure, was always associated with a marked reduction of renal flow, but a marked reduction of femoral flow was encountered in six of eight dogs. The only exceptions to the reduction in flow following hypertensive stimuli were unchanged renal flow during carotid occlusion and a transient early increase in femoral flow coincident with the peak of the pressor response following levarterenol and angiotensin.

Relation of Blood to Vascular Resistance

Following most of the procedures reported above, if blood flow is reduced vascular resistance is increased. One of the exceptions is constriction of the aorta, which permits consideration of simultaneous autoregulation of the renal and femoral beds. The femoral bed’s resistance always declined more than that of the renal bed. This capacity to dilate in the face of a reduced perfusion pressure has been considered one of the cardinal attributes of the renal circulation. Therefore it is surprising to note that in the above experiments, the femoral bed demonstrates a larger reduction in resistance than the renal bed. The activation of baroreceptors during aortic constriction may induce reflex vasodilatation which can, in turn, supplement the local “autoregulation” mechanism. Bretylium failed to alter the resistance changes, so that nervous factors can be eliminated. Evaluating the role of humoral factors and extravascular factors such as interstitial pressure changes in determining these regional resistances was beyond the scope of these experiments.
The reduced resistance of the femoral bed following hemorrhage provides another exception to the observation that vascular resistance is increased following reduction of blood flow. The anomalous behavior of femoral flow following hemorrhage is not unexpected. Following severe acute bleeding in rats this was noted to occur. The metabolic demands of the femoral bed may determine this response. On one occasion blood was reinfused shortly after bleeding. The femoral bed, although it was presumably in the resting state, underwent a rapid several-fold increase in flow above control, whereas the kidney flow gradually returned towards the control value.

Vascular Resistance Related to Reflexes

The above experiments indicate that chemoreceptor (anoxia) and baroreceptor (common carotid, occlusion) mediated reflex activity had a greater effect on femoral than on renal resistance. Hartmann, Ørskov, and Rein, using a thermostromuhr, demonstrated this on common carotid occlusion. Baroreceptor-induced vasoconstrictor activity has been said to involve skeletal muscle and intestines more than kidney or skin. Bernthal demonstrated the participation of the former two regions in chemoreceptor-induced reflex vasoconstriction. This discrete involvement of regional flows is at variance with the older view that sympathetic discharge was diffuse. Similarly, there is evidence of central nervous system representation of regional vascular control.

Vascular Resistance Related to Centrally Induced Nervous Stimuli

In the present work, a diffuse discharge, presumably involving all regions dependent upon autonomic nervous influence, is effected by increased intracranial pressure. The response of regional flows to increased intracranial pressure must be due in major part to nervous factors, for it is rapid in onset, less than two seconds in some instances. Furthermore, it is reversed by bretylium in every case. Thus, if circulating catecholamines were a primary cause of this response, it should be uninfluenced by this drug. The renal circulation is capable of responding to nervous influence almost to the point of cessation of flow. The observed differences in response of a regional flow to nervous stimuli invite recognition of different neural organization. The central representation of regional autonomic nervous control remains to be delineated for most vascular beds.

Vascular Resistance Related to Humoral Stimuli

Hemorrhage, in this instance acute bleeding, will elicit vasoconstrictor activity as well as liberation of catecholamines. Hemorrhage produced consistently an increase in renal resistance, whereas femoral resistance decreased moderately. The persistence of increased renal resistance after bretylium advances humoral factors as the more important. This observation is consonant with (a) that of Taylor and Page, who demonstrated that the response of the denervated kidney in tourniquet shock is at least partly humorally determined, and (b) the significant outpouring of epinephrine during hemorrhagic shock. Levarterenol and angiotensin consistently effect a greater increase in renal than in femoral resistance. The effect of angiotensin and
This record characterizes the renal and femoral responses to levarterenol and angiotensin. The femoral flow response is usually biphasic, whereas the renal flow response is not.

Levarterenol upon renal resistance approaches or equals that of increased intracranial pressure. The concentrations of levarterenol are not physiological, if one assumes the maximal output of catecholamines from the adrenal medulla of the cat to be 5 $\mu$g./Kg./min. The initial increase in femoral flow is not reflex in origin. Further support of this view is offered by bretylium's failure to influence the biphasic pattern of the femoral flow to levarterenol.

Intravenously administered isoproterenol consistently produced a reduction in femoral flow which is secondary to: (a) the reduction in blood pressure; (b) the reflex vasoconstriction subsequent to (a). These effects are sufficient to overcome the local vasodilator effect. The reduction in femoral flow was abolished by bretylium, presumably by its preventing reflex vasoconstriction of baroreceptor origin.

The decreased renal resistance induced by isoproterenol is in keeping with the observation that isoproterenol may cause a mild dilation of the renal vasculature.

Additional weight is given to the renal vascular action of isoproterenol, in view of its hypotensive effect causing an increase in renal resistance through baroreceptor-mediated reflex nervous activity, which is presumably offset by the local effect of isoproterenol on kidney vessels.

**Summary**

Simultaneous and continuous recording of venous flow (rotameter) of a femoral and renal bed of the dog revealed dissimilar responses in these regions. Bilateral common carotid occlusion and hypoxia (5 per cent oxygen) cause a greater increase in femoral resistance than in renal resistance. Conversely, levarterenol and angiotensin produce a greater increase in renal than in femoral resistance. Bleeding is associated with resistance changes in opposite directions, the renal bed's resistance increasing, the femoral bed's decreasing. Aortic constriction causes a reduction in the resistance of each bed; the femoral bed's resistance is reduced significantly more than the renal vascular resistance. These results suggest that the femoral bed is more reactive than the renal following baroreceptor- or chemoreceptor-induced changes. In contrast, the renal bed is more susceptible.
RENAL AND FEMORAL BLOOD FLOWS

to hormonal stimuli. To those stimuli reducing perfusion pressure, renal blood flow is more likely to be compromised.

Acknowledgment

We are grateful to Dr. Calvin F. Kay and Dr. Francis C. Wood for critically reviewing the manuscript.

References


Effect of Unilateral Pulmonary Artery Obstruction on Circulatory Dynamics in Dogs with Chronic Atrial Septal Defects
JOHN C. MCGIFF and DOMIKGO M. AVIADO

Circ Res. 1961;9:1327-1335
doi: 10.1161/01.RES.9.6.1327

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/6/1327

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/