THE RENAL HUMORAL PRESSOR MECHANISM IN MAN.

II. THE EFFECT OF TRANSITORY COMPLETE CONSTRICTION OF THE HUMAN RENAL ARTERY ON BLOOD PRESSURE AND ON THE CONCENTRATION OF RENIN, HYPERTENSINOGEN, AND HYPERTENSINASE OF RENAL ARTERIAL AND VENOUS BLOOD, WITH ANIMAL OBSERVATIONS[1]

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Complete constriction of the renal artery in animals has been shown to give rise to the liberation of a pressor and vasoconstrictor substance in the renal venous blood on re-establishment of the renal circulation (1 to 12). This pressor substance recently has been identified unequivocally as renin (6). It seemed of importance to ascertain if the same procedure in human beings would liberate renin. Accordingly, in 5 patients at operation, renal arterial and venous blood was assayed for renin before and after constriction of the renal artery. The hypertensinogen and hypertensinase contents of the blood samples were likewise estimated. Similar studies have been carried out on 6 dogs for comparison with the human observations.

METHOD

Of the 5 patients studied, 4 had renal stones and 1 had hydronephrosis. In each instance, renal function, as estimated by the blood urea nitrogen and phenolsulphonephthalein tests, was essentially normal. Operation was carried out under ether anesthesia after preoperative medication with morphine and atropine. After the surgical procedure was completed, the renal vessels were exposed. Thirty to 40 ml. of blood were withdrawn from the renal vein and from the renal artery into syringes containing 3 or 4 ml. of 4 per cent sodium citrate. Bleeding from the site of puncture was easily controlled by gentle nonconstrictive pressure. The blood was immediately transferred to centrifuge tubes which were packed in ice. The renal artery was then completely constricted by a clamp for a period of 10 to 12 minutes. Immediately on removing the clamp, 30 to 40 ml. samples of blood were withdrawn first from the renal vein and then from the renal artery. Blood pressure was recorded before, during, and after constriction of the renal artery by a Baumanometer applied to the arm.

A similar procedure was followed in dogs weighing 9.5 to 16 kgm., 2 under ether anesthesia, and 4 anesthetized with nembutal (0.04 gram per kgm. of body weight). Morphine (0.17 mgm. per kgm.) and atropine (0.01 mgm. per kgm.) were administered intramuscularly before ether anesthesia. The order of the procedure was modified as follows:

The left kidney was approached through the flank and the renal artery and vein exposed. A sample of blood was obtained from the femoral instead of the renal artery. The renal artery was occluded by a clamp for 12 minutes. About 1 minute after releasing the clamp, another sample was obtained from the femoral artery. After a minimum of 15 minutes, the renal artery was again clamped for 12 minutes and samples of renal venous blood were obtained before and immediately after releasing the clamp. Blood pressure was usually recorded continuously in the carotid artery by means of a cannula connected to a mercury manometer. In some instances, the effect of a period of 12 minutes of complete renal ischemia on the blood pressure was made without withdrawing blood samples in order to avoid the depressor action of hemorrhage.

When cold, the blood samples were centrifuged. None of the human plasma samples showed evidence of hemolysis, although most of those from the dogs showed faint hemolysis. In the first 3 human cases, the results on the renin content of blood have been omitted because the technic used was misleading and unreliable. In the last 2 cases, however, and in all the animal experiments, the renin concentration of 5 to 10 ml. of plasma was determined by the direct method (13), modified (14). The specificity of the methods was indicated by a pressor response from the tube which had been incubated, while essentially no change in blood pressure resulted from injection of the unincubated tube. Results are expressed in cat units (14).

Hypertensinogen in human plasma was determined by the above mentioned method.

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TABLE I

Effect in patients of 12 minutes of complete ischemia of one kidney on blood pressure and concentration of renin, hypertensinogen, and hypertensinase in plasma from renal artery (RA) and renal vein (RV)

Case	Blood pressure		Renin				Hypertensinogen				Hypertensinase				
	Before clamping	After release	Before		After		Before		After		pH of incubation	Before		After	
			RA	RV	RA	RV	RA	RV	RA	RV		RA	RV	RA	RV
	mm. Hg		*cat units per 10 ml. plasma*				*cat units per ml. plasma*					*dog units per ml. plasma*			
1. K. L.	135/85	118/75					3.4	3.4	3.0	2.8	7.3	1.0	1.0		
2. E. S.	122/74	117/76					6.8	5.7	6.5	5.9	7.3	1.2	1.2	1.2	1.0
3. D. H.	88/43	78/40					2.4	2.8	2.1	2.6	7.3	1.5	1.4	1.4	1.5
4. I. F.	135/76	121/74	0	0	0	1.2	3.5	3.2	2.8	2.4	7.3	1.4	1.4	1.9	1.5
											4.5	1.2	1.4	0.9	1.0
5. F. B.	123/85	119/90	0	0	0	0.2	3.7	5.7	4.8	6.5	7.3	1.2	1.2	1.1	1.1
											4.5	1.3	1.2	1.1	1.2

Hypertensinase was determined by a modified method (15, 16). In 2 cases, hypertensinase was determined at a pH of 4.5 instead of 7.3 because renal hypertensinase has been reported to have optimal activity at or near this acidity (17).

RESULTS

The concentrations of renin, hypertensinogen, and hypertensinase, in plasma from the renal artery and vein, and the blood pressure, before and after constriction of the renal artery, in the 5 patients are summarized in Table I, and the renin concentration and blood pressure in dogs, before and after clamping the renal artery, are shown in Table II.

Blood pressure. Neither during the 12-minute period of complete ischemia of one kidney, nor for at least 15 minutes after re-establishment of the renal circulation, was there a significant rise in blood pressure in either the human or dog experiments (Figures 1 and 2). After the above procedure in dog 6, the kidney was decapsulated and the renal artery clamped for 2½ hours. Following release of the clamp, the blood pressure rose 30 mm. Hg and gradually returned to its initial level over the course of about 30 minutes.

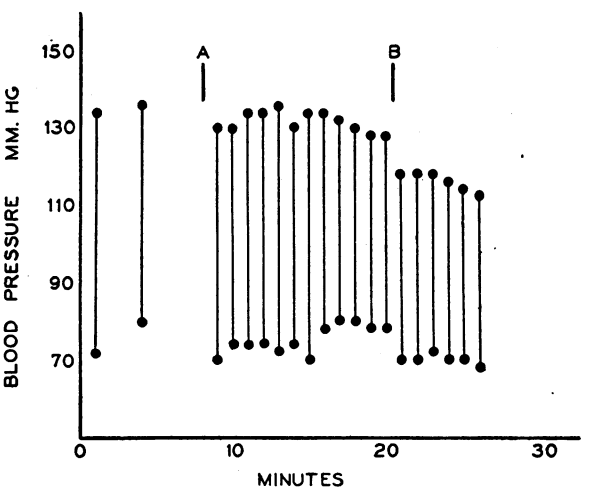

FIG. 1. EFFECT OF CLAMPING ONE RENAL ARTERY ON THE BLOOD PRESSURE OF PATIENT I. F.

The patient was under ether anesthesia. At A, one renal artery was completely occluded. At B, the clamp was released. The interval between A and B was 12 minutes. Note that no rise in blood pressure occurred after the clamp was removed.

TABLE II

Effect in dogs of complete ischemia of one kidney on blood pressure and concentration of renin in plasma from systemic artery (SA) and renal vein (RV)

Dog	Anesthetic	Duration of complete ischemia	Blood pressure		Renin			
			Before clamping	After release	Before		After	
					SA	RV	SA	RV
		minutes	*mm. Hg*		*cat units per 10 ml. plasma*			
1	Ether	12	122	80	0.8	1.4	0.4	2.0
2	Ether	12	130	125	0	0	0	0.3
3	Nembutal	12	112	105	0.5	1.0	0.3	0.8
4	Nembutal	12	120	120	0.2	1.1	0.1	0.8
5	Nembutal	12	115	110	0	0	0	0
6	Nembutal	12	108	105	0.2			0.5
		150	105	135			1.6	2.1

Renin. In the human cases, no renin was detected in renal venous or arterial plasma before or in plasma from the renal artery a minute or so after release of the clamp. In both cases,

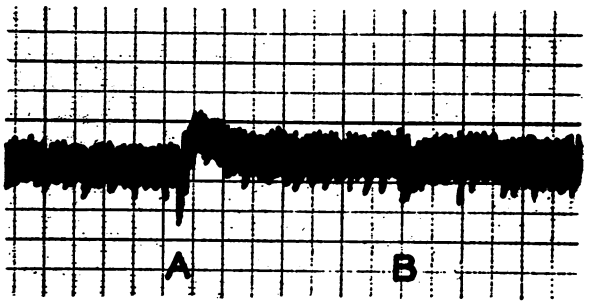

FIG. 2. EFFECT OF CLAMPING THE RENAL ARTERY ON THE CAROTID BLOOD PRESSURE OF DOG 4

The dog was under nembutal anesthesia. At A, one renal artery was clamped. At B, the clamp was released. The interval between A and B was 12 minutes. Note that no rise in blood pressure occurred after the clamp was removed.

however, small amounts of renin were found in the plasma from the renal vein immediately after the re-establishment of the circulation through the kidney (Table I, Figure 3). In dogs, essentially similar results were obtained except that renin was frequently demonstrable in the renal venous and to a less extent in the renal arterial blood before the period of renal ischemia and it was only in the 2 etherized dogs that a definite (but slight) increase in the amount of renin was found after 12 minutes of complete ischemia. In dog 6, after 2½ hours of complete renal ischemia, large amounts of renin were found in both femoral arterial and renal venous blood when the renal circulation was re-established. This finding is in accord with other studies (6).

Hypertensinogen. Hypertensinogen values were found to be normal and similar in both renal arterial and venous blood before and after renal artery constriction in the human subjects, with the exception of case 5 where values in renal venous plasma were higher than those in the plasma from the renal artery.

Hypertensinase. In the human beings, no significant differences in the concentration of hypertensinase, either before or after clamping of the renal artery, were detected in the renal arterial and venous blood when determined at a pH of 7.3 in 4 cases and at 4.5 in 2 cases.

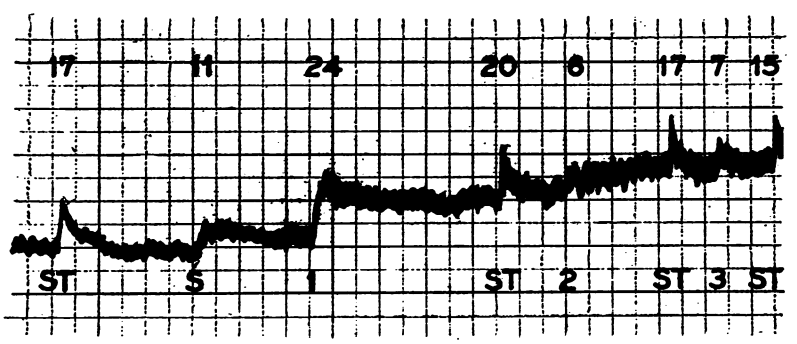

FIG. 3. DEMONSTRATION OF RENIN IN THE RENAL VENOUS PLASMA OF PATIENT I. F. AFTER CLAMPING THE RENAL ARTERY FOR 10 MINUTES

The patient was under ether anesthesia for the removal of renal stones. The blood pressure curves shown above are those of a cat under dial anesthesia. The figures above the curves indicate the rise in blood pressure in mm. Hg.

ST: Response to the intravenous injection of 0.5 cat unit of standard hypertensin.

S: Response to 11 ml. of physiological saline.

1. Response to incubated sample equivalent to 5 ml. of renal venous plasma. When calculated for renin and the control subtracted, this is equivalent to 1.2 cat units of renin per 10 ml. plasma. The tube was prepared as described elsewhere (15) and incubated for 4 hours at 37° C.

2. Response to unincubated control equivalent to 5 ml. of plasma.

3. Response of hypertensinase control equivalent to 5 ml. of plasma.

The presence of renin is indicated by a pressor response from the incubated sample (tube 1) and lack of significant pressor action from the unincubated (tube 2) and hypertensinase (tube 3) controls.

DISCUSSION

Most investigators have employed a period of complete ischemia of several hours for producing a rise of blood pressure on re-establishing the renal circulation in animals. One author (3) has shown that unless the kidney is decapsulated during the period of ischemia, hypertension does not usually occur when the clamp on the renal artery is released because of the collateral circulation through the capsule. Others (8), however, found a pressor effect from complete renal ischemia for 30 minutes. In our experiments in dogs and human beings, complete ischemia of one kidney for 12 minutes produced no rise in blood pressure after removal of the constriction from the renal artery. It was obviously neither feasible nor safe to decapsulate the kidneys of our patients or to employ long periods of complete ischemia. In dog 6, with renal decapsulation and 2½ hours of complete ischemia of the kidney, re-establishment of the renal circulation was shown to produce a pressure rise of 30 mm. Hg.

Although no blood pressure rise occurred following the 12-minute period of complete ischemia, small amounts of renin were detectable in the renal venous blood of the 2 patients; *i.e.*, 0.2 and 1.2 cat units per 10 ml. of plasma, respectively. Since the secretion of renin after renal blood flow becomes normal is presumably short lasting, such amounts theoretically would not be sufficient to cause a rise in systemic blood pressure.

In dog 1 under ether anesthesia, small amounts of renin were present in the systemic and renal venous blood before the renal artery was clamped. We have observed the presence of renin in the systemic blood not infrequently in animals, but not in man, under various types of anesthesia. In the dog, renin appeared in considerable amounts (2.0 cat units per 10 ml. plasma) in the renal venous blood when the clamp was first removed at the end of 12 minutes of complete ischemia, but the total amount of renin produced by the kidney was small as indicated by the fact that the systemic (renal arterial) blood concentration of renin did not perceptibly increase. This is in contrast to dog 6 in which, after 2½ hours of complete ischemia, a rise of 30 mm. Hg in blood pressure was observed and 2.1 cat units of renin were found in 10 ml. of renal venous plasma. In this animal, the total amount of renin produced by the kidney was much greater, however, as evidenced by a systemic blood titer of 1.6 cat units of renin per 10 ml. of plasma.

In dog 2, under ether anesthesia, only a small amount of renin was found in the renal venous blood after release of the clamp.

In the nembutalized dogs, the results were less regular in that there were no clear-cut changes in the amount of renin in the respective samples of systemic and renal venous bloods before and after clamping, although the renal venous blood samples always contained more renin than the femoral arterial samples, except in dog 5 where no renin was detected in the blood at any time.

These results in animals are entirely in harmony with the human observations, namely that in response to 12 minutes of complete ischemia of one kidney, the blood pressure does not rise on re-establishment of the renal circulation and that the increment of increase of renin liberated into the blood stream by way of the renal vein is small and is either just barely detectable or undetectable by the method employed.

In the present experiments, no difference was found in the concentration of hypertensinogen in the plasma from renal artery and renal vein, either before or after constriction of the renal artery in patients. Furthermore, we have repeatedly found normal concentrations of hypertensinogen in the plasma of patients with hypertension (18 to 20). We have no explanation for the high concentration of hypertensinogen in the plasma from the renal artery and for the normal values from the renal vein in case 5.

The hypertensinase activity of nonhemolyzed plasma samples was determined at a pH of 7.3, the optimal pH for the activity of hypertensinase in plasma (15), and in 2 cases at pH 4.5 which has been described (17) as about the optimal pH for the activity of the hypertensinase of kidney. No significant difference in its concentration in renal arterial and venous blood was noted either before or after renal arterial constriction. There was, therefore, no indication of a liberation or disappearance of hypertensinase in the renal venous blood as a result of complete constriction

of the renal artery for 12 minutes. In plasma of the systemic blood of patients having elevated arterial pressure, the concentration of hypertensinase has been found to be the same as in normal individuals (21).

One author (22) found that in dogs, after prolonged partial constriction of the renal artery, the hypertensinase content of plasma from the renal vein was distinctly less than that from the renal artery. Differences between our results and his may possibly be due to his use of periods of prolonged partial ischemia in dogs and our employing a short period of complete ischemia in human beings.

The present study in no way indicates the rôle the kidney may play in human hypertension. It does, however, demonstrate that, in response to constriction of the human renal artery, renin is liberated from the kidney into the systemic circulation by way of the renal vein. There was no indication in human beings that either blood hypertensinase or renal hypertensinase was removed from the plasma by the kidney or produced by the kidney as a result of a short period of complete constriction of the renal artery. It is concluded that the renal humoral pressor mechanism is present in its entirety in man and that it is stimulated to activity by constriction of the renal artery as in animals.

SUMMARY

1. Complete constriction of the renal artery in 5 patients and in 6 dogs, for a period of 12 minutes, produced no rise of blood pressure after release of the clamp but did liberate small amounts of renin into the renal venous blood of the 2 patients in whom it was estimated and in 2 of 6 dogs.

2. In patients, the concentration of hypertensinogen was the same in the renal arterial and venous blood, before and after constriction of the renal artery, with one exception; hypertensinase, determined at a pH of 7.3 and 4.5, was likewise the same.

3. These observations demonstrate that by constriction of the renal artery in man, the renal humoral pressor mechanism is stimulated to activity as in animals.

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