Serioangiographic Study of Renal Cortical Necrosis Induced by Administration of Estrin and Vasopressin in Rats

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We report a serioangiographic method in rats which permits assessment of the course and dimensions of the renal arteries, the durations of the arterial and venous phases, and the intensity and uniformity of the renal parenchymal filling. The procedure was employed to study the mechanism by which administration of vasopressin to rats pretreated with estrin leads to renal cortical necrosis. The pathogenetic significance of the spasm localized on the larger renal arteries was proved directly; the possible role of the arteriovenous shunt in the development of the renal ischemia was excluded.

Key words: renal cortical necrosis, serioangiography, estrin, vasopressin, renal vasoconstriction.

HUMAN RENAL CORTICAL NECROSIS occurs most frequently as a complication of pregnancy.[5,6,20,25] It is assumed that roles are played in the development of the disease by hyperestrinism, by the vasoactive substances released because of the relatively large loss of blood, and hence by the pituitary hormones.[1-3,9,11,12,22] We have constructed a renal cortical necrosis model with the aim of studying the mechanisms of action of the hormones.[14] After administration of vasopressin to rats pretreated with estrin, bilateral renal cortical necrosis could be observed in every animal. We have previously reported that circulatory disturbances of the kidney can be well examined by means of an angiographic method.[13,15,17] We have since made improvements in our procedure, and by using serioangiography we have obtained detailed information about the renal vessels.

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Received August 11, 1977 and accepted for publication April 16, 1979.

Materials and Methods

Serioangiographic Method

Each rat was anesthesized with ether, and the right common carotid artery was exposed by the paratracheal approach. A polyethylene cannula (OD/ID = 0.8/0.5 mm) was inserted into the carotid lumen to the level of the aortic arch, and 1.0 mg of heparin was injected through this cannula to prevent blood clotting.

Uromiro, a 75% aqueous solution of N,N'-diacetyl-3, 5-diamino-2, 4, 6,-triiodobenzoic acid methylglucaminate (Bracco Industria Chimica, Milano, Italy) was used as contrast material, in a quantity of 1.5 ml per rat.

During administration of the contrast material, photographs were taken with a Siemens Tridoros 5 S apparatus under the following conditions: focus distance 70 cm; 48–50 KVP, 160 ma; exposure time 0.01 seconds. A Reiser-Gärtner automatic cerebral cassette changer, and Ilford film were used, together with a programme changer, a 24 × 30 cassette, and a Siemens filter. This apparatus, plus the insertion of a fine grid, enabled us to obtain a total of eight exposures at intervals of 0.5–5.0 seconds. The time-programming for the film series on the treated animals depended on the expected pathologic differences.

0020-9996/79/0700/0295/$00.75

TABLE 1.

Serial Number	Number Rats	Body Weight (g)	Pretreatment	Inducing Injection	Time after Vasopressin (min)	Grade of Renal Vasoconstriction†				Arteriovenous Time (sec)	Grade of Defect in Parenchymal Filling†			
						0	1+	2+	3+		0	1+	2+	3+
1	12	193.1±6.3*	—	—	—	12	—	—	—	2.0	12	—	—	—
2	12	185.6±4.7	Estrin	—	—	12	—	—	—	2.0	12	—	—	—
3	6	192.4±7.1	—	Vasopressin	30	—	6	—	—	2.0	6	—	—	—
4	6	189.3±5.2	—	Vasopressin	60	1	5	—	—	2.0	6	—	—	—
5	12	196.5±6.4	Estrin	Vasopressin	30	—	—	—	12	5.0	—	—	—	12
6	12	187.2±4.5	Estrin	Vasopressin	60	—	—	2	10	5.0	—	—	3	9
7	12	195.0±7.4	Estrin	Vasopressin	24 h	11	1	—	—	1.5	2	9	1	—

* Standard error of the mean.
† Grading: 0, no change; 1+, slight change; 2+, medium change; 3+, considerable change.

Experimental Groups

The examinations were carried out on male albino R-Amsterdam rats weighing 180–250 g, kept on a standard diet. The control group consisted of 12 animals who were not given any treatment prior to the experiment.

The pretreated group consisted of 60 rats, each of which received the following preparations: 1 mg/day of estrin acetate (Hogival, Chinoin) for 10 days administered subcutaneously; 10 IU of synthetic lysin vasopressin (Sandoz), given once, subcutaneously.

The treatment procedure and the more relevant observations are listed in Table 1. The grades of renal vasoconstriction and defect in parenchymal filling were determined in a semiquantitative manner and are denoted by plus signs.

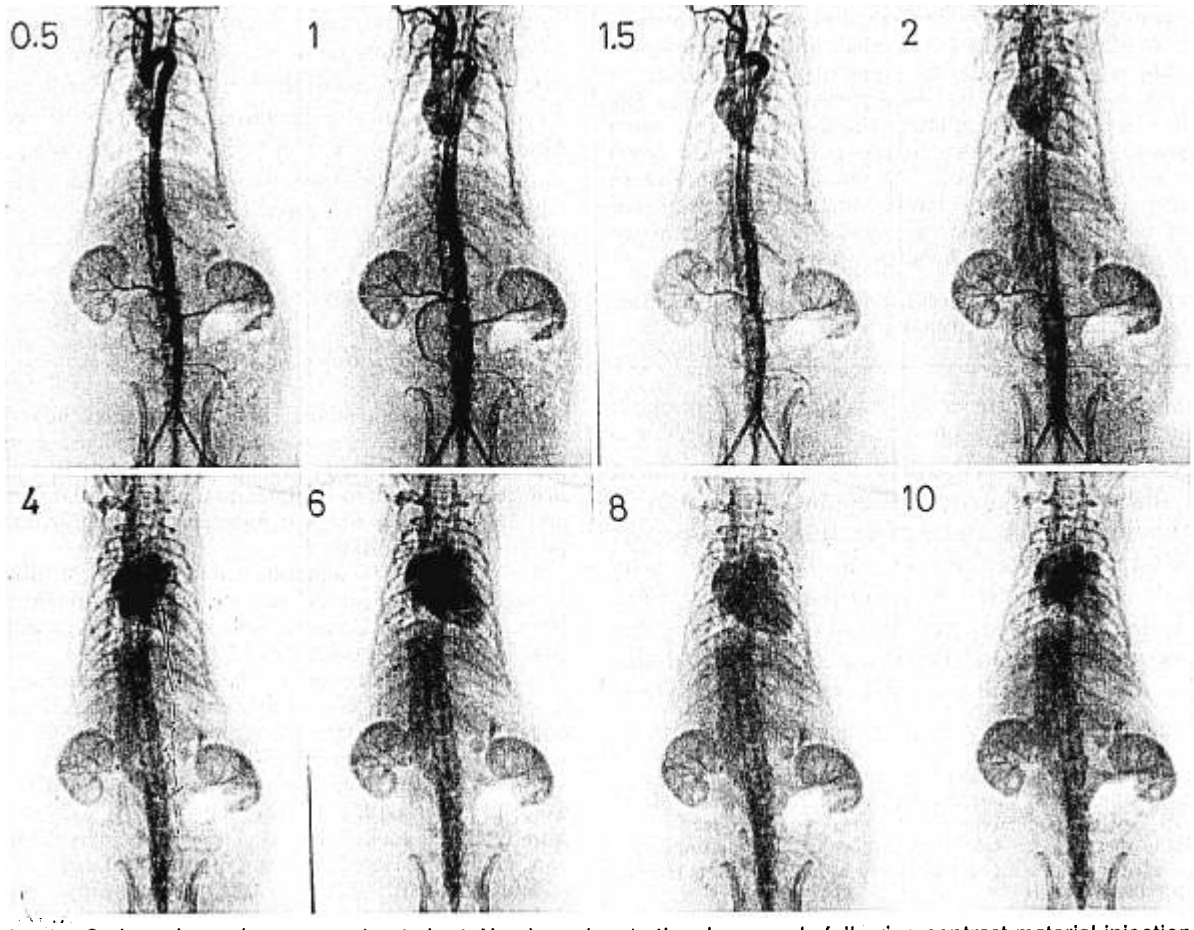

Fig. 1. Serioangiography on an untreated rat. Numbers denote time in seconds following contrast material injection.

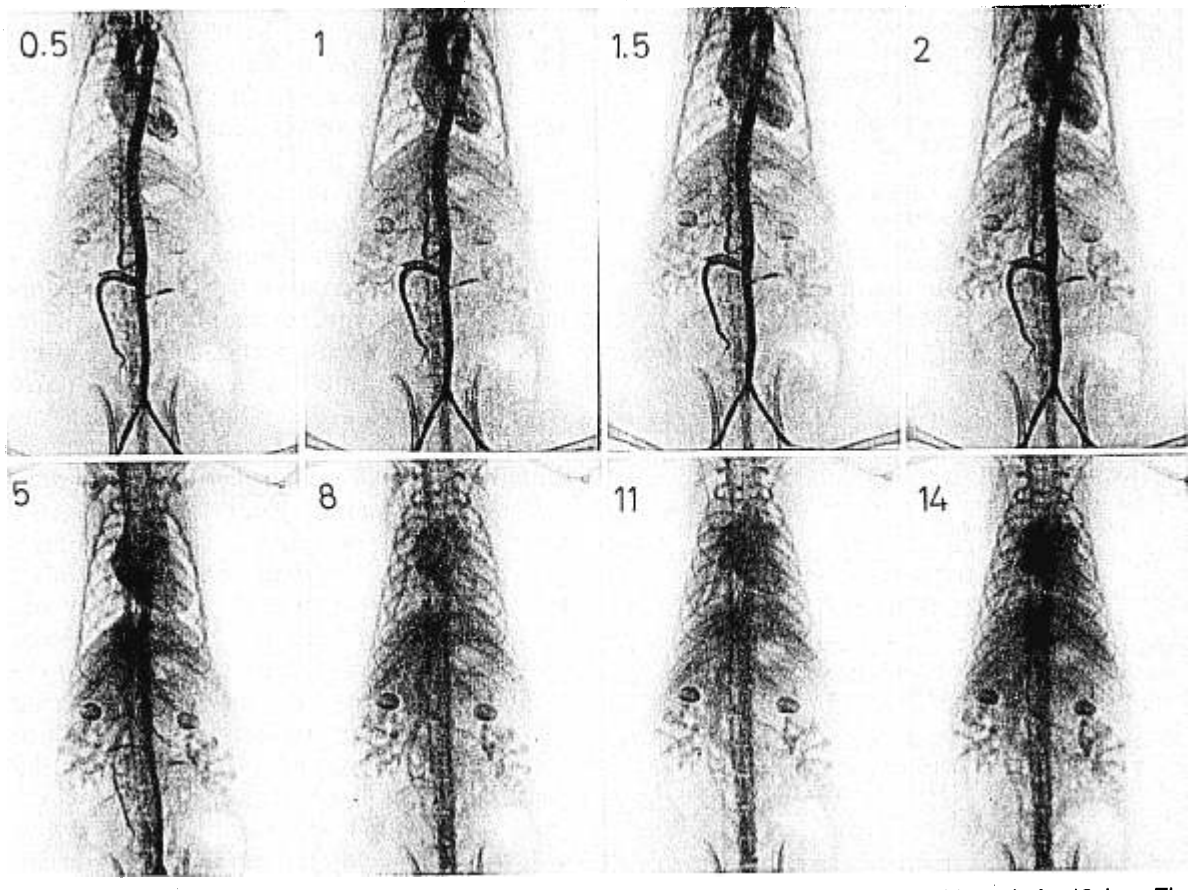

Fig. 2. Serioangiogram taken 30 minutes after administration of vasopressin to a rat pretreated with estrin for 10 days. The spasm of the main renal arteries is marked. The arterial period is considerably lengthened. Infarction-like absences of shadow can be observed in the renal parenchyma. Numbers denote time in seconds following contrast material injection.

The evaluation was performed "blind," by an individual unaware of the pretreatment.

Results

Control Group

Figure 1 shows serioangiograms on the control rats. In the arterial phase, 0.5–1.0 seconds, one can clearly see a short section of the right common carotid artery, the complete length of the aorta, the iliac arteries and the renal arteries, which divide into interlobar branches and can be followed throughout within the shadow of the kidneys; the arborization outline gives the network of smaller arteries stemming from these. After 2 seconds, the outlines of the inferior vena cava and the renal veins are beginning to appear. The exposure after 2 seconds therefore corresponds to the transitional stage, since arteries too can still be seen in addition to the initial venous filling. In those serioangiograms after 4–10 seconds only the venous filling can be observed, with decreasing intensity. As a consequence of the nephrographic effect, the shadows of the kidneys are differentiated from their environment even on the first photograph; in the control animals, the parenchymal filling is uniform throughout.

Pretreated Group

The serioangiograms of the animals treated only with estrin agree in every respect with those of the untreated control rats. Without estrin pretreatment, vasopressin results in a temporary, slight renal vasospasm.

The differences observed after estrin plus vasopressin administration are each illustrated by one typical serioangiogram. Angiograms taken 30 minutes after administration of vasopressin to rats pretreated with estrin (Fig. 2) demonstrate very marked and characteristic differences compared to the controls in the filling of the renal arteries, in the blood transit time and in the parenchymal effect. The duration of the arterial phase is substantially longer: adequate filling can be seen in

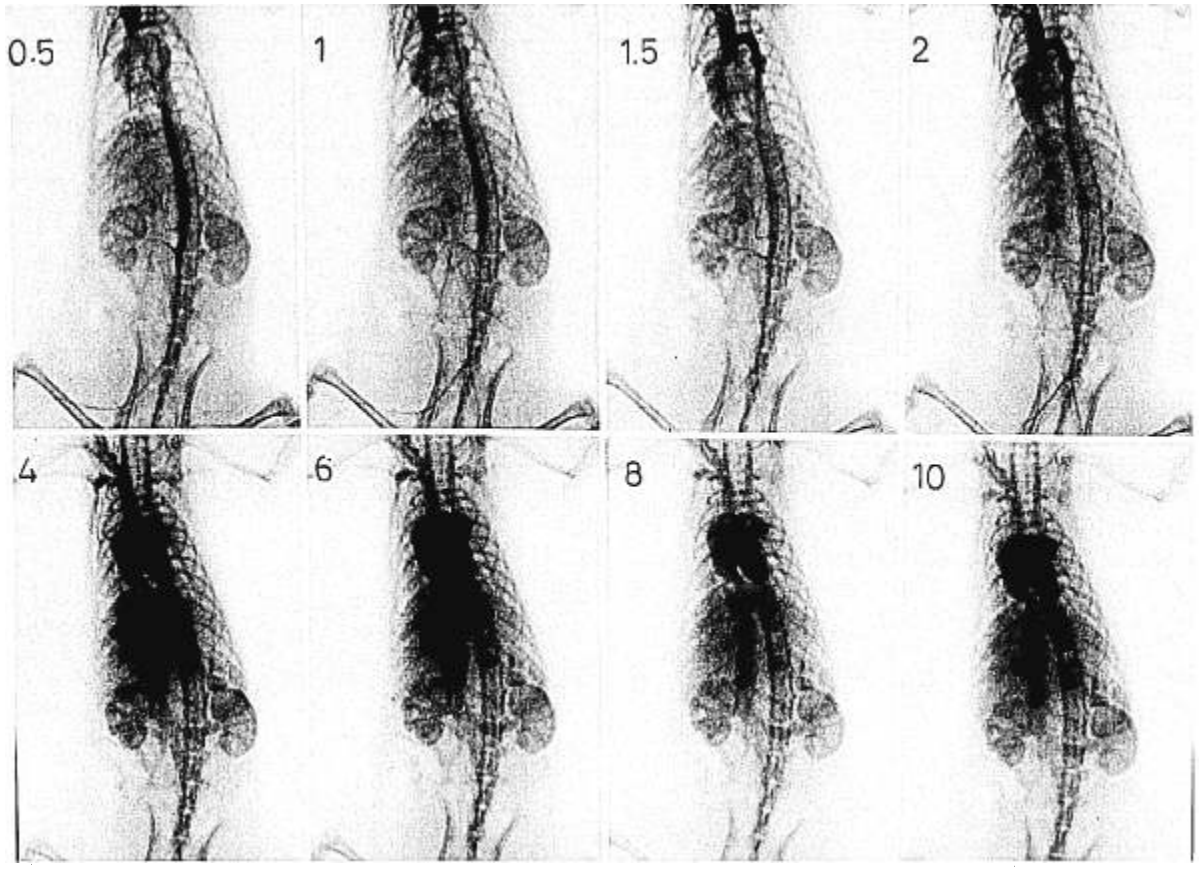

Fig. 3. Serioangiogram taken 24 hours after administration of vasopressin to a rat pretreated with estrin for 10 days. The renal arteries have normal dimensions. The parenchymal filling is somewhat fainter, and displays a slightly patchy filling. Numbers denote time in seconds following contrast material injection.

the aorta and the renal arteries even on the fifth photograph, taken after 5 seconds, and the very faint renal veins can be perceived only on the 8-second exposure; the filling of the renal veins can be seen on the last two photographs. The pictures of the arterial phase show the right renal artery to be intensively and uniformly filled, whereas there is a short stricture in the initial section of the left renal artery. The branching of the renal arteries and the interlobar arteries are scarcely visible and are markedly spastic. A nephrographic effect can be observed along their course, and large, triangular, infarction-like areas without contrast can be detected between them in the parenchyma. The first pictures show contrast material reflux in the left ventricle. Above the kidneys, the adrenals are strikingly enlarged as a consequence of the estrin treatment. There were similar changes in the estrin-pretreated rats 60 minutes after administration of vasopressin.

After 24 hours the renal circulation is almost the same as in the control animals (Fig. 3). The renal arteries and the interlobar arteries have normal dimensions. On the photograph taken after 1.5 seconds, the renal veins are already opacifying. The arteries can no longer be seen on the 4-second picture, but the larger intrarenal veins, the renal veins and the inferior vena cava are well outlined. The shadow of renal parenchyma is somewhat fainter than in the control animals, and exhibits a slight degree of patchy filling. In the subcapsular cortex, mainly on the right side, a marked wedge-shaped parenchymal effect can be observed.

Discussion

Arteriography on living rats was reported first by our group,[17] and later by Salamon,[23] Ekelund and Olin,[8] Kreel et al[16] and Ekelund et al.[7] The method was deficient in that it permitted only one to two moments of the blood circulation to be recorded. The serioangiographic procedure yields a detailed definition of the full perfusion cycle of the two kidneys, similar to that routinely obtained in the clinical field.

Following several days of estrin treatment, the administration of vasopressin to rats is known to cause characteristic morphological changes and bilateral

renal cortical necrosis.[1,2,14] Since vasopressin alone in the dose employed did not cause any significant renal changes, it may be assumed that estrin sensitizes the renal vessels to the vasoconstrictive effect of vasopressin. Our view is supported by the examinations by Lloyd,[18] Lloyd and Pickford,[19] and Deis et al,[4] who observed that the vasopressor effects of the posterior pituitary hormones are manifested more intensively in estrin-pretreated animals. No matter how obvious this hypothesis appears, a direct confirmation of the renal vasospasm was missing. Our present examinations clearly demonstrate that vasopressin induces a considerable vasospasm localized to the larger renal arteries in rats pretreated with estrin. The significant vasoconstriction can be brought into a causal correlation with the development of renal cortical necrosis. This effect of estrin is selective, referring only to the renal vessels. The different renal arteries have varying sensitivity to vasopressin. This can explain the focal character of the necrosis, and the fact that certain tissues are not subject to the general ischemic effect. The exact mechanism of the sensitization is unknown.

The results of our serioangiographic examinations permitted us to exclude the pathogenetic role of the arteriovenous shunt in the renal cortical necrosis induced by this hormone treatment. Following the now classic description by Trueta,[27] the possibility of a shunt has repeatedly been raised in the medical literature dealing with the question.[10,24,26] The Trueta phenomenon assumes the shortening of the arteriovenous time. Our series of examinations, however, shows that the duration of the arterial phase is substantially lengthened and the beginning of the venous filling is considerably delayed compared to the control animals. A similar observation was reported by Moreau et al,[21] on the basis of their angiographic examinations of humans with renal cortical necrosis.

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