Peri-Ureteric Collateral Vessels in Rabbits with Experimental Renal Hypertension

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SUMMARY

The development of collaterals to an ischemic kidney was studied in rabbits with two-kidney Goldblatt hypertension. Hypertension was produced by applying a silver clip of 0.9 mm in internal diameter on the left renal artery with the right kidney intact. Peri-ureteric collaterals were found at autopsy in 27 (32.9%) of 82 animals that were killed 7 days (early stage) and in 30 (40.5%) of 74 animals that were killed in more than 70 days (late stage) after clipping. The average blood pressure was 123.8 ± 2.6 (SE) mmHg in animals with collaterals vs. 125.3 ± 2.1 mmHg in animals without them in the early stage, and 142.5 ± 4.4 mmHg in animals with collaterals vs. 122.6 ± 3.3 mmHg in animals without them in the late stage. These results indicate that the collaterals to an ischemic kidney develop independently of the rises in blood pressure during the first week and the presence of collaterals is associated with moderate to severe hypertension in the late stage.

Additional Indexing Words:
Collateral circulation Experimental hypertension Ischemic kidney Renovascular hypertension

COLLATERAL vessels to an ischemic kidney are demonstrated in about half of patients with renovascular hypertension by angiographic studies. The type and the incidence of collateral vessels have been extensively studied in radiologic aspects.1)–6) The presence of collateral vessels has been considered to reflect a significant gradient of blood pressure between a proximal and a distal segment of the stenosed renal artery. However, it remains obscure how early and how rapidly the collateral vessels develop in those patients, because almost all angiographic studies have been based on hypertensive patients with long-standing occlusive diseases of the renal artery. An early development of collateral vessels to an ischemic kidney was accidentally observed in a patient who had suffered from a sudden occlusion of the renal artery.

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during an extensive surgical procedure.7) The present experiments were attempted to study the incidence of collateral vessels to an ischemic kidney in rabbits with experimental two-kidney Goldblatt hypertension.

**Method**

Male rabbits weighing 2.0 to 2.5 Kg were fed a standard diet for the rabbit (CR 1, Japan Clea Ltd). After a control period of 2 weeks the left renal artery was constricted by a silver clip of 0.9 mm in internal diameter, the right kidney being left intact. Eighty-two animals (short term group) were killed 7 days and 74 animals (long term group) were killed in more than 70 days after clipping of the renal artery. An average period of observation was 124 days for the latter. A sham operation was performed in 31 animals (sham operation group), which were killed 7 days after surgery. Blood pressure and body weight were recorded every day during the post-operative first week and at weekly intervals thereafter. Blood pressure was measured by an indirect method on the central ear artery.8) The operative procedures were performed through a small flank incision under pentobarbital anesthesia (30 mg/Kg, iv). The presence or absence of peri-ureteric collateral vessels were confirmed at autopsy. Collateral vessels were tortuous, coiled and dilated as compared with the vessels along the contralateral ureter. Pelvic, capsular and other types of collateral vessels were occasionally observed, but the peri-ureteric ones were more prominent. The present study dealt with only the peri-ureteric ones.

**Results**

Peri-ureteric collateral vessels were not found in any of 31 animals that had suffered from sham operation, but they were observed in 27 (32.9%) of 82 animals (short term group) which were killed 7 days, and in 30 (40.5%) of 74 animals (long term group) which were killed in more than 70 days after clipping of the renal artery. Although the collateral vessels appeared more extensive in individual animals of the long term group than in those of the short term group, the difference in incidence of the collateral vessels was statistically not significant between the 2 groups. Typical peri-ureteric collateral vessels were illustrated in Fig. 1 (short term group) and Fig. 2 (long term group).

Fig. 3 shows relations between blood pressure and the presence or absence of peri-ureteric collateral vessels. Blood pressure of an individual animal was expressed with an average of the blood pressures during the last 3 days in both the sham operation and the short term group and with that obtained during the last 3 weeks in the long term group. The sham operation group had an average blood pressure of 96.4±1.7 (SE) mmHg with a range of 72 to
Fig. 1. Peri-ureteric collateral vessels in a rabbit that was killed 7 days after clipping of the renal artery.

Fig. 2. Peri-ureteric collateral vessels in a rabbit that was killed 98 days after clipping of the renal artery. Capsular collateral vessels are also seen.

Fig. 3. Blood pressure in rabbits with and without collateral vessels. Closed circles represent animals with collateral vessels and open circles represent those without collateral vessels.
115 mmHg. In the short term group an average blood pressure increased to 123.8±2.6 mmHg with a range of 98 to 151 mmHg in 27 animals with peri-ureteric collateral vessels and to 125.3±2.1 mmHg with a range of 95 to 174 mmHg in 55 animals without them. There was no significant difference in average blood pressure between animals with and without collateral vessels. In the long term group an average blood pressure markedly increased to 142.5±4.4 mmHg with a range of 96 to 188 mmHg in 30 animals with peri-ureteric collateral vessels but remained at 122.6±3.3 mmHg with a range of 87 to 168 mmHg, which approximately corresponded to the values of the short term group, in 44 animals without peri-ureteric collateral vessels. In contrast to the short term group there was a significant difference in average blood pressure between animals with and without peri-ureteric collateral vessels (p<0.01). The incidence of blood pressure more than 130 mmHg was 73.3% (22 of 30) in animals with peri-ureteric collateral vessels but was 34.1% (15 of 44) in animals without them. The difference in the incidence was also highly significant (p<0.001).

Fig. 4 shows weight ratios of the left to the right kidney separately according to the presence or absence of peri-ureteric collateral vessels. The weight ratio was approximately 1.05 in the sham operation group but it decreased in most of the animals with clipping of the left renal artery. In the short term group an average of the weight ratios was 0.88±0.02 with a range of 0.62 to 1.11 in the 27 animals with peri-ureteric collateral vessels and was 0.93±0.01 with a range of 0.62 to 1.15 in the 55 animals without them. The

Fig. 4. Weight ratio of the left to the right kidney in rabbits with and without collateral vessels. Closed circles represent animals with collateral vessels and open circles represent those without collateral vessels.
difference in the average weight ratio was not significant between the 2 subgroups. In the long term group the weight ratio was very low in some animals. An average of the weight ratios could not be calculated in this group because of a skewed distribution. The incidence of weight ratio of less than 0.7 was 73.3% (22 of 30) in the animals with peri-ureteric collateral vessels but was 43.2% (19 of 44) in the animals without them. The difference in incidence was significant between the 2 subgroups (p<0.02).

DISCUSSION

The presence of collateral vessels to an ischemic kidney and its clinical significance have been well discussed in patients with renovascular hypertension.1)-6) However, little attention has been paid to the time-course of development of the collateral vessels. The rapidity of development of the collateral vessels may not have been determined in patients in whom the stenotic process of the renal arteries is gradual. Only an exceptional observation provides an important clue. Love and Bush7) angiographically demonstrated in a patient that collateral vessels to the ischemic kidney appeared as early as 8 days after a sudden occlusion of the renal artery.

A few experimental studies have been reported on collateral vessels to an ischemic kidney. Mason et al9) observed a large peri-ureteric collateral vessels in a dog in which the renal artery had completely been occluded. An angiographic study on the patterns of collateral flow in renal ischemia was conducted by Abrams and Cornell11) and was continued by Takahashi et al10) in an small group of dogs in which the left renal artery had been constricted after right nephrectomy. They found a few clearly identifiable collateral vessels to the ischemic kidneys in 2 dogs on the first, in 2 dogs on the third, in a dog on the sixth, and in 2 dogs on the ninth days after constriction. The collateral vessels developed progressively into an extensive network after 10 to 15 weeks. However, the incidence of collateral vessels was not determined in these studies, because 7 of 12 animals died of uremia in 2 to 6 days after constriction.

The present study was designed to observe the incidence of collateral vessels to an ischemic kidney in rabbits with two-kidney Goldblatt hypertension. Hypertension was produced by clipping of the renal artery with an intact contralateral kidney. This procedure has been established as a method to produce a persistent rise of blood pressure in rabbit.11) This type of experimental hypertension (two-kidney Goldblatt hypertension) seems to be more favorable to the present study, because it has a greater similarity to the human renovascular hypertension than hypertension produced by clipping of the renal
artery with contralateral nephrectomy (one-kidney Goldblatt hypertension). In addition animals with this type of hypertension survive for a long time without uremia.

In the present experiments collateral vessels to an ischemic kidney developed in 32.9% of animals as early as 7 days after clipping of the renal artery. The rapidly developed collateral vessels may represent dilatation of pre-existing, nonfunctioning channels as emphasized by Flasher et al. In the long term group, the incidence of collateral vessels was 40.5%, which did not significantly differ from that in the short term group. These results indicate that almost all collateral vessels develop in the early stage and that they extend slowly in the subsequent stages. An average of blood pressure increased approximately to 125 mmHg independently of the presence or absence of periureteric collateral vessels in the early stage, but its subsequent increase was observed more in animals with collateral vessels. These results show that the presence of the collateral vessels is associated with moderate to severe hypertension in the late stage, although there may be no definite cause and effect relationship between the two. The weight ratio of the left to the right kidney had no particular relationship with the presence or absence of periureteric collateral vessels in the early stage, but it was lower in the animals with collateral vessels than in those without them in the late stage. These results show that the collateral blood supply is not sufficient to keep the weight of an clipped kidney normal. Otherwise, it is better to say that the presence of such a moderate ischemia that leads to a contracted kidney may stimulate the development of collateral vessels.

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References