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ORIGINALS

Changes in Blood Flow and Vasculature of the Dog Kidney Undergoing Normothermic and Hypothermic Ischaemia*

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Summary. In 11 mongrel dogs both kidneys have been subjected to a 2 h ischaemic period. One kidney was cooled by perfusing the renal artery at 4° C while the contralateral normothermic kidney was clamped for 2 h. Studying the renal blood flow using the Xenon wash out technique, sequential renal scanning and angiography, marked differences between hypo- and normothermic ischaemia kidneys were observed. One or two hours following hypothermic perfusion a marked decrease of blood flow in the first compartment and vasoconstriction was evident, while within this period following normothermic ischaemia an enhanced renal blood flow was observed. After 24 h renal blood flow and renal function tested by ^{131}I-Hippuran clearance returned to normal values. Angiographic studies corresponded to the preoperative findings. In contrast, normothermic ischaemia kidneys showed a decreased renal blood flow, impairment of kidney function in isotope studies and pathological angiographic changes.

Key words: Hypothermia - Ischaemia - Renal blood flow - Xenon wash out technique - Sequential renal scanning.

Renal surgery which requires clamping of the renal pedicle cannot exceed 30-40 min under normothermic conditions without damage to the renal parenchyma. To prolong this period selective intravascular cooling of the kidney has been performed (2, 4, 12, 13). Previous experimental and clinical data have shown that selective hypothermic perfusion effects a significant prolongation of ischaemic tolerance as indicated by biochemical and radioisotope studies (6, 7).

In these studies there was clearcut evidence that, although the hypothermic perfusion results in a reduction of renal function immediately following surgery, within twenty-four hours all parameters have returned to normal (Fig. 1). The aim of these studies was to elucidate the mechanism of this reversible loss of function.

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METHODS

Surgery

Eleven mongrel dogs with an average body weight of 20 kg., were anaesthetised intravenously with 25 mg/kg body weight Pentobarbitol and intubated. Following a midline incision both kidneys were mobilised and the renal pedicle was prepared. Using the Seldinger technique, a catheter was introduced into the left renal artery and fixed with a tourniquet. Thereafter the kidney was perfused with a solution consisting of 500 ml of 5% Dextran 40, 500 ml isotonic saline and 500 IU heparin which had been cooled to 4° C as described previously (6). During the 10 minutes perfusion of the left kidney the circulation of the right kidney was stopped by clamping the renal pedicle with a De Bakey clamp. The ischaemic time of each kidney was two hours. After releasing the clamps the abdomen was closed in layers.

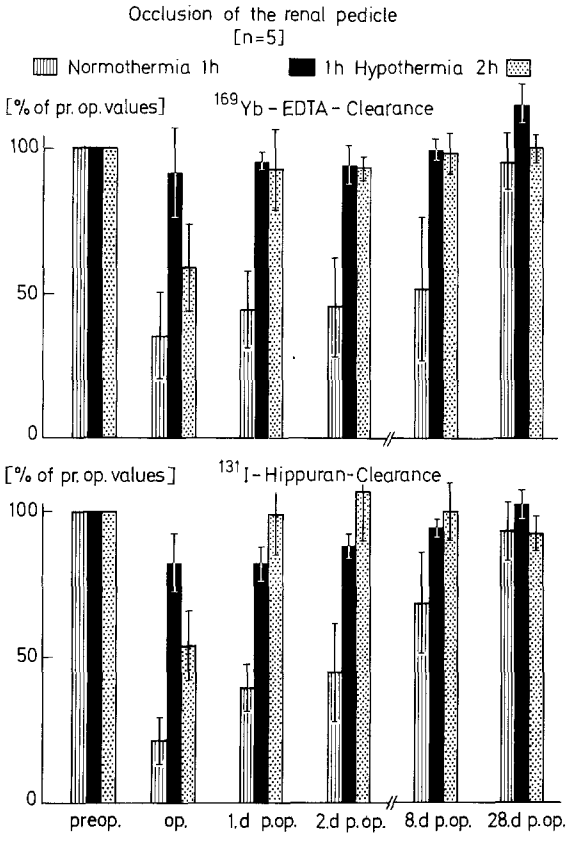

Fig. 1. Changes of EDTA- and Hippuran clearance in the postoperative course, given in percentage of the initial values

MEASUREMENTS

Estimation of Blood Flow and Analysis of the Compartments

100 µ Ci xenon dissolved in 0.1 ml saline was injected via a selective renal artery catheter. After injection the catheter was removed immediately. The blood flow studies were performed preoperatively and then 60 and 120 min and 24 h after reestablishment of the renal circulation. The xenon washout was read by a external scintillation probe during a 50 min period. A compartment analysis was performed on the obtained xenon washout curves. Specific flows were calculated using the formula:

$$Fs = \frac{\ln 2}{MLT}$$

Fs = specific flow
= distribution ratio blood-renal parenchyma
ln = natural logarithm
MLT= Mean life time (= Half time for each compartment)

The absolute flow was derived from the flows in individual compartments, expressed as a percentage of the total flow and from the specific flow (3, 10, 11).

Sequential Renal Scanning with a Scintillation Camera

In addition, kidney function was measured using sequential renal scanning with a scintillation camera according to the "region of interest" method. The procedure and calculation have been described previously (6, 9).

Angiographic Studies

Angiographic X-ray studies using Conray(R) 60 % were performed prior to surgery and 2 and 24 h after release of the vascular clamps in order to elucidate changes in the vascular structure of kidneys exposed to ischaemia.

RESULTS

Renal Blood Flow (RBF) Measurements

Preoperative Findings. Prior to surgery an average total renal blood flow of 447 ± 90 ml/min/100 g was measured which was composed of 339 ± 84 ml/min/100 g in the first compartment and 108 ± 24 ml/min/100 g in the second compartment (Table 1).

RBF Following Two Hours of Normothermic Perfusion

Ischaemia. A marked increase of the RBF was observed one and two hours after releasing the clamps, the values being 597 + 165 ml/min / 100 g after one hour and 633 ± 157 ml/min/100 g after two hours.

Twenty four hours after surgery the total renal blood flow was reduced to 349 ± 30 ml/min/100 g mainly due to the perfusion in the first compartment being reduced to 206 ± 63 ml/min/100 g. Flow in the second compartment increased to 143 ± 42 ml/min/100 g.

Following normothermic ischaemia there was therefore an overall reduction of total RBF to 78 % of the initial values. This was due to a relative increase of the perfusion of the second compartment to 132 % while the first compartment was reduced to 60.5 % of the initial values (Table 2a).

RBF Following Two Hours of Hypothermic Perfusion

One hour after releasing the clamps the first compartment was detectable in only one kidney. The total RBF in this kidney (547 ml/min/100 g) was normal. RBF in the other hypothermic perfused kidneys was reduced to 334 ± 35 ml/min/100 g due to the lack of the first compartment.

Table 1. Distribution of renal blood flow. Total renal blood flow and distribution in untreated mongrel dogs (n = 11)

	sF_1	sF_2	Ao_1	Ao_2	aF_1	aF_2	tF
	ml/min/100g		%		ml/min/100g		
Mean	675	220	71.6	23.2	339	108	447
SD	107	51	5.99	4.84	84	24	90

A_o - percentage of total flow into the compartment
sF - specific flow (ml/min/100 g)
aF - total flow of individual compartment (ml/min/100 g)
tF - total renal blood flow $\hat{=} F_{a1} + F_{a2}$
A third compartment was not claculated

Table 2a. Total renal blood flow and distribution, following two hour normothermic ischaemia

			sF_1	sF_2	Ao_1	Ao_2	aF_1	aF_2	tF
t	n=		ml/min/100g		%		ml/min/100g		
30 min	1		522	154	67.9	15.7	292	68	360
60 min	5	Mean	848	270	73.4	21.3	478	119	597
		SD	141	25	12.9	11.6	209	48	167
120 min	9	Mean	870	247	79.3	14.8	540	93	633
		SD	190	33	6.6	5.4	165	17	157
24h	4	Mean	578	241	53.8	38.2	206	143	349
		SD	173	13	14.7	14.1	63	42	30

t = time after releasing the clamps

Measurement after two hours showed 6 out of 9 kidneys still without the first compartment, while 3 kidneys had an RBF of normal range (444 ± 68 ml/min / 100 g). This lack of the first compartment reduced the average total renal blood flow to 254 ± 100 ml/min / 100 g in the other kidneys. After 24 h all the investigated kidneys reached their initial values with a mean value of 455 ± 75 ml/min / 100 g (Table 2b).

Radioisotope Studies with ^{131}I-Hippuran
Clearance studies performed on both kidneys three hours following ischaemia, showed bilateral delayed accumulation of the labelled material. In the perfused kidneys there was a complete return to normal after 24 h (Fig. 1). In contrast, the normothermic ischaemic kidneys revealed a curve characteristic of accumulation of isotope without an excretion phase (Fig. 2).

Angiography. Angiographic studies performed on normothermic ischaemic kidneys one hour after reestablishment of blood circulation showed a marked shortening of transit time of the contrast and an early demonstration of the renal vein (Fig. 3). Angiography demonstrated partially thrombosed renal arteries in the two kidneys which did not show a shorter

Table 2b. Total renal blood flow and distribution, following two hour hypothermic period

			sF_1	sF_2	Ao_1	Ao_2	aF_1	aF_2	tF
t	n=		ml/min/100g		%		ml/min/100g		
30 min	1		-	209	-	88.9	-	209	209
60 min	4	Mean	-	334	-	83.5	-	334	334
		SD		35		4.3		35	35
120 min	1		653	261	85.0	12.6	476	71	547
	6	Mean	-	254	-	87.3	-	254	254
		SD		41		5.2		41	41
	3	Mean	614	241	69.2	22.2	341	103	444
		SD	34.5	25	10.8	10.2	98	30	68
24h	4	Mean	628	227	69.9	21.3	353	102	455
		SD	51	25	13.6	9.9	112	43	75.5

t = time after releasing the clamps

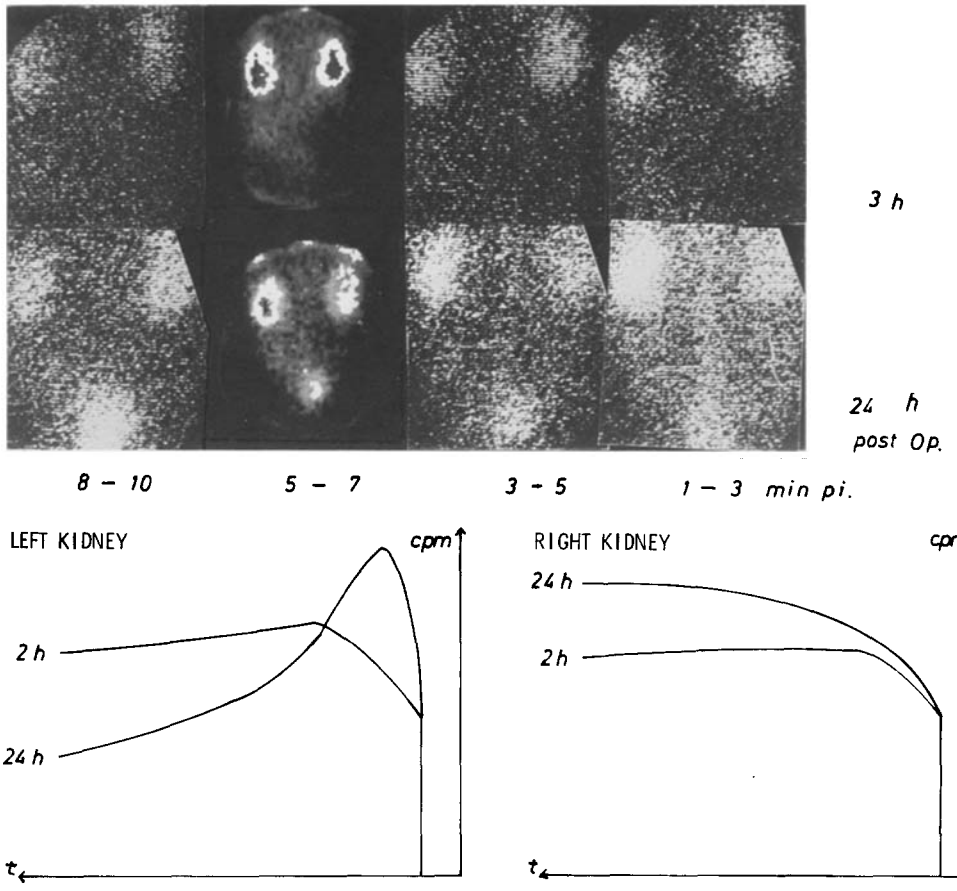

Fig. 2. Radioisotope studies using ^{131}I-Hippuran following two hours normothermic ischemia (right kidney) and two hours hypothermic ischemia (left kidney)
Above: Sequential scintigram read 3 and 24 hours after surgery
Below: Isotope renograms obtained by the region of interest technique

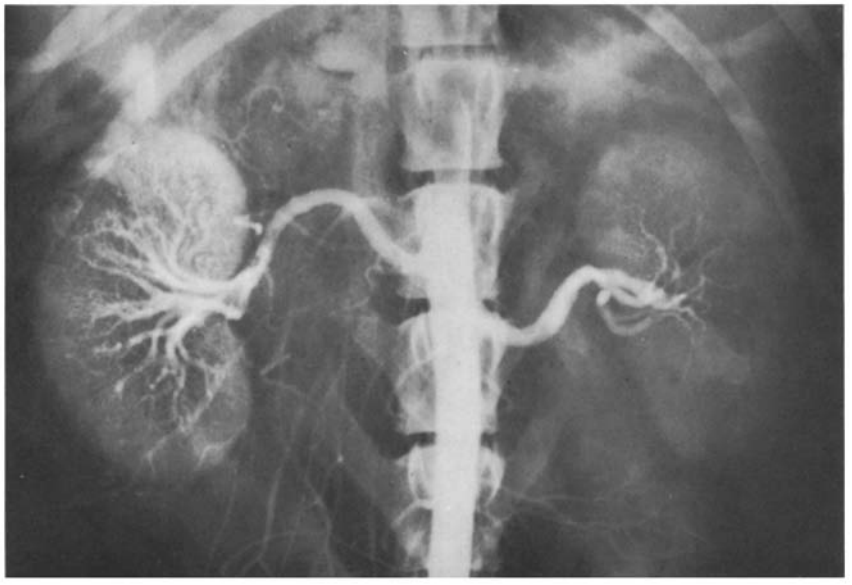

Fig. 3. Arteriogram (dog P_{10}) 2 hours after normothermic ischaemia (right) and hypothermic perfusion (left)

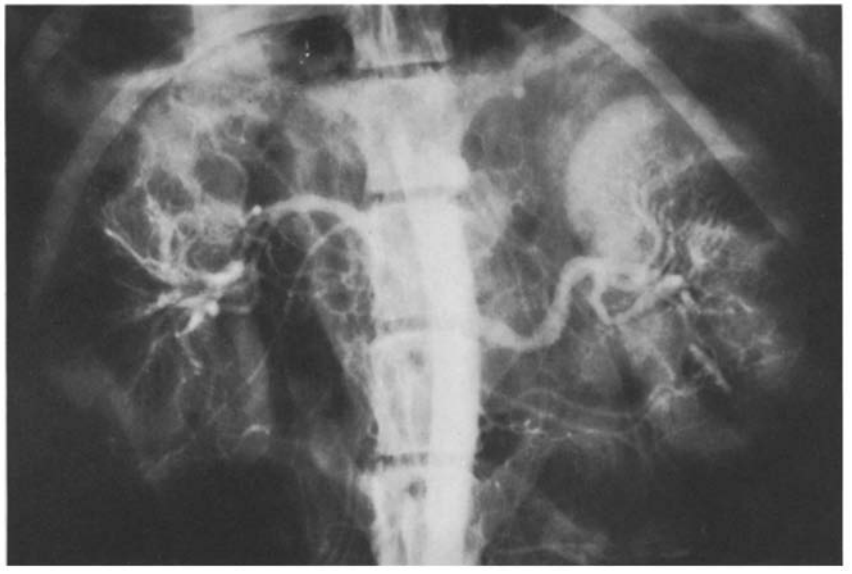

Fig. 4. Arteriogram (dog P_{10}) 24 hours following surgery

transit time. The segmental and interlobar arteries of the other kidneys were dilated and in the parenchymal phase the uptake of contrast of the kidney was patchy and the corticomedullary junction was ill-defined. Only one kidney was shown to excrete contrast in the late exposures.

At 24 h, more than half of the normothermic ischaemic kidneys showed angiographic evidence of decreased renal blood flow. Segmental and interlobar arteries were of normal calibre (Fig. 4). In 86% of these cases however there was a relative narrowing of the arcuate arteries and in the parenchymal phase the uptake of contrast was patchy. Again, excretion of contrast was demonstrated in only one kidney.

Angiograms performed one or two hours after reestablishment of circulation to the hypothermic perfused kidneys clearly demonstrated a longer transit time of contrast combined with a narrowing of the segmental and interlobar arteries (Fig. 3). The arcuate arteries however were visualised very poorly, if at all. In the parenchymal phase uptake of contrast by the renal cortex was homogeneous and the corticomedullary junction could be seen. Two thirds of these kidneys excreted contrast medium.

At 24 hours the angiograms of all these hypothermic perfused kidneys showed a normal vasculature and parenchyma and normal excretion of contrast medium (Table 3, Fig. 4).

DISCUSSION

The benefit of hypothermic selective perfusion of the kidney in order to avoid tissue damage due to ischaemia has been shown in previous

Table 3. Differences between normothermic and hypothermic ischaemic kidneys related to the angiographic findings. The observed changes are given as percentage of the animals tested

Ischaemia	t	n=	RBF		Aa. interlobares		Aa. arcuatae	Parenchyma	Corticomedullary junction	Excretion
			increased	reduced	dilated	constricted	constricted	patchy	ill defined	observed
Normothermic	I. Day	11	82%		91%		95.5%	100%	91%	9%
Hypothermic	I. Day	12		75%		83.5%	91%	8%	-	67%
Normothermic	II. Day	7		57%		43%	86%	86%	86%	14%
Hypothermic	II. Day	4		Normal		Normal	-	-	-	100%

experimental and clinical studies. It was shown that following two hours of hypothermic ischaemia transient impairment of kidney function appeared which was reversible within 24 hours. The reported experiments provide evidence that after this period renal blood flow also returns to normal values as shown by flow measurement using the xenon washout technique. The architecture of blood vessels in angiographic studies performed 24 h after surgery corresponds to the preoperative findings. In contrast to these hypothermic perfused kidneys, normothermic ischaemia caused diminution of renal blood flow at 24 h mainly due to a decrease of perfusion in the first compartment.

One and two hours following hypothermic perfusion, however, a marked decrease of blood flow in the first compartment is evident and this is associated with vasoconstriction as indicated by angiography. Nevertheless, 75% of these kidneys showed excretion of the contrast medium. Although the renal blood flow in normothermic ischaemic kidneys is enhanced only one of them showed excretion of contrast medium. From these results it can be concluded that there is a marked discrepancy between the increased postoperative renal blood flow and the lack of excretion capacity in the normothermic ischaemic kidneys. These findings seem to demonstrate that in the kidney that develops acute tubular necrosis following hypotension, impairment of renal function cannot be attributed to the changes of renal blood flow alone.

The fact that normal function is restored to healthy kidneys 24 h after hypothermic perfusion does not necessarily imply that the same results can be obtained when abnormal kidneys are exposed to such a period of hypothermia. The value of vasodilators in overcoming the initial vasoconstriction is worthy of consideration (1, 5, 8) but, because of the cardiogenic effect of these drugs which would be administered systemically by our in situ perfusion technique, we have so far avoided their use.

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