Urological Research 3, 177-182 (1975)

Compensatory Renal Hypertrophy
II. During Contralateral Hydronephrosis

An Experimental Study in Dogs

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Received: June 11, 1975; and in revised form: September 29, 1975

Summary. Compensatory renal hypertrophy and hyperfunction during contralateral chronic hydronephrosis was investigated. It was found that graded impairment of the function in hydronephrotic kidneys causes proportional compensatory hypertrophy and hyperfunction in the contralateral normal kidney. The functional pattern both "per kidney" and "per nephron" was the same in the kidneys investigated here and in kidneys where contralateral nephrectomy had been performed, but whereas a decreased ability to concentrate the urine maximally and to reabsorb sodium was encountered in the latter, this could not be detected in this study. On the other hand, a decreased C_{OSM} in the diseased kidney did not stimulate a corresponding increase in the contralateral kidney as did unilateral nephrectomy. Adaptive and growth dependent changes in compensatory renal hypertrophy are discussed.

Key words: Compensatory renal hypertrophy, Dogs, Hydronephrosis, Clearances.

During unilateral hydronephrosis the contralateral kidney undergoes compensatory hypertrophy, the degree of which depends upon the severity of the hydronephrotic process. This is a well established morphological fact (6, 5). Edvall (1959) has demonstrated a compensatory increase in Inulin and p-amino Hippurate clearances (C_{IN} C_{PAH}) in a human kidney during contralateral partial obstruction (3). Hoeg (1962) showed that the function of a resected kidney in humans and dogs was proportional to its percentage share of the total kidney mass (8). Does the normal kidney adjust its function in an inversely proportional way to the function of a diseased contralateral kidney, where nephron loss is caused by a pathological process such as hydronephrosis?

This investigation has two objects. The first is to obtain an answer to the above question. The second is to elucidate the functional patterns in the normal kidney and in the contralateral hydronephrotic kidney.

Material and Methods

Eight female mongrel dogs weighing from 14 to 18 kg were used. The exact age of the dogs was unknown, but it was estimated to range from two to six years at the start of the study. The animals were fed the same diet throughout the study. Four dogs were followed for 15 months, one for 1 year, one for 24 weeks, and 2 for 16 weeks.

Surgical Technique

Chronic hydronephrosis was established, using a technique described in a previous publication (12). An ureterostomy was made on the hydronephrotic side allowing separate urine collection from the two kidneys. A Chevassu ureteric catheter was used for urine collection from the hydronephrotic side to ensure complete collection.

Clearance Methods

The clearance methods and analytical methods used in this study were identical to those described and discussed in a previous article (14). The clearance observations were done before and at regular intervals after the surgical procedure.

Intravenous pyelography was used to visualise the renal outline and the site of the partial obstruction. Drip-infusion pyelography, ac-

cording to the method of Wendt (1965), was used exclusively (19). One ml of 50% sodium diatrizoate per kilogram body weight was mixed with an equal amount of 5% dextrose in water and infused intravenously over a period of 8 to 10 min. Pyelograms were obtained 3, 6, and 9 min following the start of the infusion, and at 10, 30 and 60 min following the end of the infusion.

Renal size was estimated according to the method of Olesen and Genster (1970) (13). The maximal renal length, as measured on the pyelograms, was cubed, and the volume of the kidney was estimated by means of a nomogram.

Results

Hydronephrosis of various degrees developed, but the animals could be divided into two groups. One group (A) consisted of two animals in which the partial ureteric obstruction rapidly resulted in contracted kidneys with pronounced hydropelvis. The rest of the dogs formed the second group (B) in which kidney damage of a lesser degree developed.

If unilateral kidney damage is almost complete, there should be no significant difference between the compensatory hypertrophy and hyperfunction which occurs in the contralateral kidney and that which occurs in a kidney following unilateral nephrectomy. Creatinine clearance (C_{Cr}), p-amino hippuric acid clearance (C_{PAH}) and maximum tubular secretion of p-amino hippuric acid (Tm_{PAH}) and the volume of kidney tissue in kidneys with severe contralateral kidney damage, moderate contralateral kidney damage, and following unilateral nephrectomy (group C) are compared in the Figs. 1, 2, 3, and 4. The results following unilateral nephrectomy are from a previously published study (14). The statistical comparisons are shown in Table 1. After the 52nd week, no statistically significant difference in any of the four parameters could be obtained between hypertrophied kidneys in group A and in group C (Table 1). The increase in C_{Cr} and C_{PAH} seems to be slower in group A than in group C, and if group A and group B are compared (Table 1), no significant difference is found within the first 12 weeks after the onset of the hydronephrosis. However, all four parameters in group A are significantly higher than those in group B after 52 weeks of hydronephrosis. A sensitivity test at the 95% level of significance shows that the present results do not reveal a difference of less than 20%. The results, therefore, do not justify any conclusion as to whether the parameters in groups A and C are identical.

Fig. 5 illustrates the functional counterbalance in GFR between a hydronephrotic and hypertrophic kidney from the same animal. Between 2 and 12 weeks, there is no correlation at all. A negative correlation is obtained during the period 52-65 weeks. Although the correlation coefficient is low it is highly significant statistically.

Table 2 shows the maximum concentrating ability (MCA) and osmolar clearance (C_{OSM}) in hydropenic dogs with unilateral hydronephrosis and contralateral normal kidneys before and after the onset of hydronephrosis. MCA in hypertrophic kidneys during the period 2-4 weeks was 1956 $\pm$ 356 mOSM/l. Whereas a significant loss of maximum concentration power was encountered during the first month following unilateral nephrectomy, no significant change occurred in this parameter following contralateral partial obstruction. It can also be seen that the clearance of osmotically active substances did not increase significantly, but that the total osmolar clearance of the hydronephrotic and hypertrophic kidneys reached a value identical to that reached by the solitary kidney following unilateral nephrectomy. Table 3 shows filtration fraction, Tm_{PAH} per unit of glomerular filtration rate (GFR), renal plasma flow (RPF) per unit of tubular mass, osmolar clearance per unit of GFR, urine flow per minute per unit of GFR, percent of filtered sodium reabsorbed, and percent of filtered urea excreted before and during compensatory hypertrophy caused by contralateral partial ureteric obstruction.

Table 1.

Parameter	Weeks	Group A v Group C	Group A v Group B
C_{Cr}	2-12		
	16-24		
	52-65	$p < 0.20$	$p < 0.05$
C_{PAH}	2-12		$p < 0.20$
	16-24	$p < 0.10$	$p < 0.10$
	52-65	$p < 0.70$	$p < 0.05$
Tm_{PAH}	2-12	$p < 0.90$	$p < 0.70$
	16-24	$p < 0.20$	$p < 0.05$
	52-65	$p < 0.50$	$p < 0.05$
Kidney Volume	2-12		$p < 0.90$
	16-24		$p < 0.02$
	52-65	$p < 0.80$	$p < 0.05$

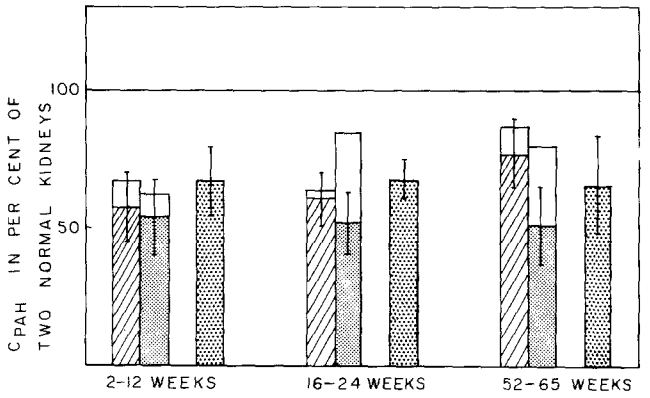

Fig. 1

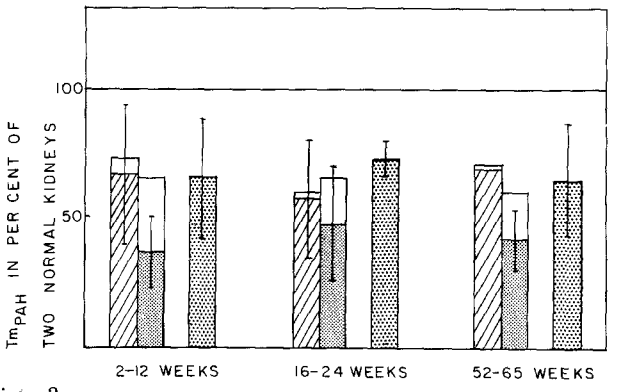

Fig. 3

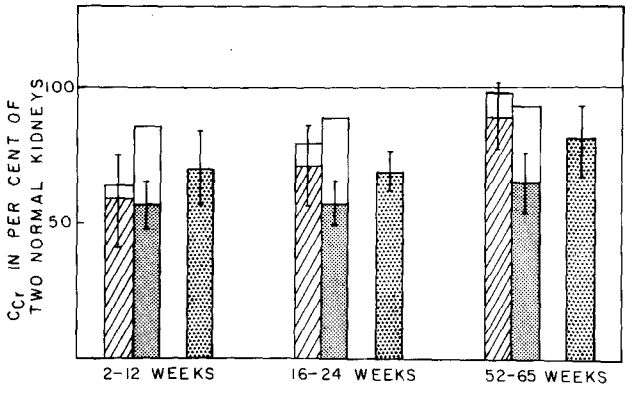

Fig. 2

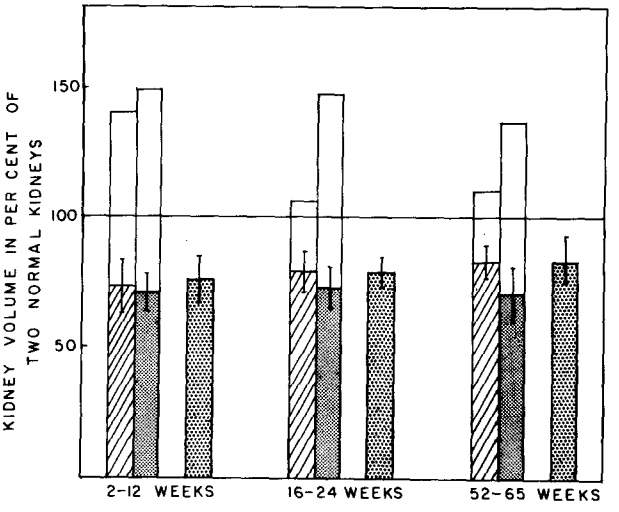

Fig. 4

Fig. 1-4. The compensatory increase of C_{PAH}, C_{Cr}, Tm_{PAH} and kidney volume (expressed in percent of two normal kidneys) during contralateral severe kidney damage (▨, group A), contralateral moderate kidney damage (▦, group B), and after contralateral nephrectomy (▩, group C). Clear bars represent the hydronephrotic kidneys

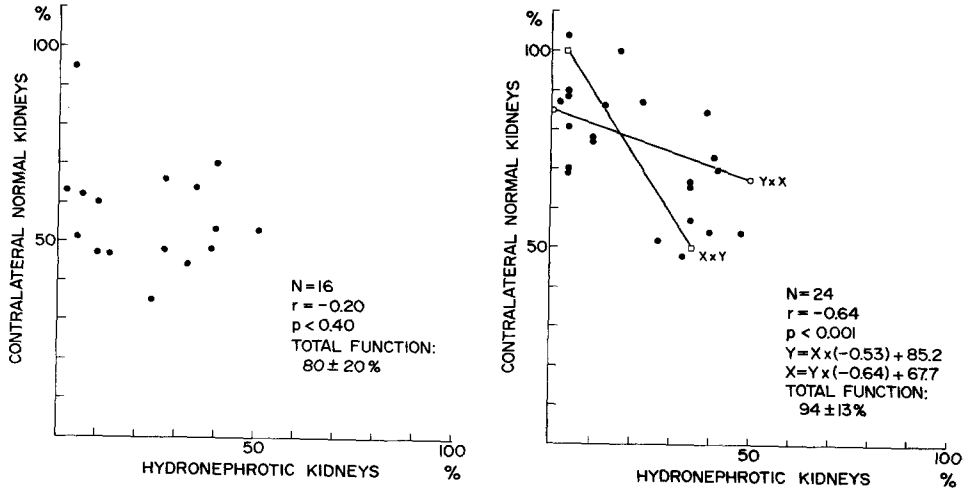

Fig. 5. The relationship between the C_{Cr} of hydronephrotic kidneys and their hypertrophic mates expressed in percent of two normal kidneys.

It can be seen that the filtration fraction is significantly increased throughout the study, that the ratio Tm_{PAH}/C_{Cr} shows a glomerular predominance and that relative hyperaemia occurs in the last part of the observation period. The osmolar clearance, expressed in percent of clearance of creatinine, was normal throughout the study. The percentage of filtered sodium reabsorbed does not alter at all.

Discussion

During chronic impairment of renal function caused by varying degrees of partial ureteric obstruction of different degrees, the contralateral kidney adjusts its function in an inversely proportional way. The functional and morphological increase in the hypertrophic kidney is slower when the hypertrophy is caused by disease in the contralateral kidney than when the contralateral kidney is removed. In addition, it can be seen from Fig. 5, that the total function of the paired kidneys does not approach the 100% level for two normal kidneys until the hydronephrosis is stable. The difference between 80 ± 20% and 94 ± 13% is statistically significant (t-test for non paired values gives a p-value less than 0.02). Throughout the study the total volumes of renal parenchyma in paired kidneys were over the 100% level for two normal kidneys.

The statistical comparisons in Figs. 1, 2, 3, and 4 would have been more conclusive with a larger number of observations, which would have increased the sensitivity of the statistical tests provided standard deviations remained unchanged. But at least some conclusions can be drawn from the present results.

First of all, it can be concluded that, there is no statistically significant difference in function and volume between a kidney with a severely damaged mate (group A), and a soli-

Table 3

Normal range		2-12 weeks	16-24 weeks	52-65 weeks
$C_{Cr}/C_{PAH}x100$	35±6	41±12	43±7	42±9
P		<0.05	<0.005	<0.10
$Tm_{PAH}/C_{Cr}x100$	22±4	22±11	15±11	17±4
P				<0.05
C_{PAH}/Tm_{PAH}	13±2	17±8	16±8	15±1
P			0.05	
$C_{OSM}/C_{Cr}x100$	5.1±1.1	5.0±1.1	5.2±1.5	4.4±0.7
P		<0.90	<0.90	<0.70
% f. Na. r.	99.7±0.2	99.4±0.3	99.4±0.3	99.6±0.2
P		<0.30	<0.30	<0.80

Table 2

	Both kidneys			Hydronephrotic kidney			Hypertrophic kidney		
	MCA mOSM/l	C_{OSM} ml/min	C_{OSM} % of 2	MCA mOSM/l	C_{OSM} ml/min	C_{OSM} % of 2	MCA mOSM/l	C_{OSM} ml/min	C_{OSM} % of 2
Before unilateral hydronephrosis	2017 ±180	3.6 ±0.6	100	2017 ±180	1.8 ±0.3	50 50	2017 ±180	1.8 ±0.3	50
2-12 weeks after	-	2.6 ±0.5	72	870 ±451	0.6 ±0.4	16	1842 ±340	2.0 ±0.5	56
16-24 weeks after	-	2.8 ±0.5	78	1011 ±470	0.8 ±0.5	18	1891 ±296	2.0 ±0.5	56
56-65 weeks after	-	2.6 ±0.8	72	785 ±437	0.6 ±0.4	16	1906 ±244	2.0 ±0.9	56

tary kidney after contralateral nephrectomy (group C). With the sensitivity of the statistical tests applied to the present results, this does not necessarily mean that the parameters are identical in the two groups but that they are very similar.

After the 52nd week, there was a statistically significant difference in function and volume between a kidney with a severely damaged contralateral mate (group A) and a kidney with a moderately damaged mate (group B). From Fig. 5b it can be seen that the y · x slope and the y-axis intersect at 85.2%. This value is close to the average of C_{Cr} 60 weeks after unilateral nephrectomy (14). Thus, a compensatory hyperfunction develops in residual nephrons, whether nephron loss is caused by surgery or disease. One must therefore remember that when compensatory renal hypertrophy is studied after nephrectomy for a diseased kidney little change may be seen because hypertrophy and hyperfunction have already developed pre-operatively (18). In this connection, it should also be mentioned that using the normal kidney as a control in studying unilateral kidney disease gives false results which will vary in proportion to the degree of damage in the experimental kidney.

With regard to the concentrating mechanism, group A and B have a different pattern from group C. No detectable change occurred in maximal concentrating ability. This may be explained by the fact that the urine excreted from the damaged kidney is dilute, thus, to accomplish water balance, excess water is excreted by the damaged kidney and not by the normal. A severe decrease of osmolarity clearance unilaterally does not stimulate a corresponding increase of the same parameter in the contralateral kidney. Apparently, as long as the osmolar clearance in the diseased kidney is approximately 1/6 of two normal ones, no increase occurs contralaterally, the total C_{OSM} being approximately identical to that of a solitary kidney after unilateral nephrectomy.

The changes of C_{Cr}/C_{PAH}, Tm_{PAH}/C_{Cr} and C_{PAH}/Tm_{PAH} are identical to those encountered in the solitary kidney. Filtration becomes increasingly efficient during the observation period, and a clear glomerular predominance is encountered after one year with contralateral kidney damage of various degrees. C_{Cr}/cm^3 of renal tissue rises from 0.75 ± 0.10 to 0.98 ± 0.20 ml/min/cm^3, and this difference is statistically significant (the p value being less than 0.05, t-test for non paired values). C_{PAH}/cm^3 of renal tissue rises from 2.15 + 0.24 to 2.34 ± 0.14, but this difference is not statistically significant. Tm_{PAH} per unit of renal tissue is unchanged being 0.16 + 0.03 and 0.16 ± 0.06 before and after 1 year of contralateral kidney damage. As stated by Bugge-Asperheim and Kiil (1968) the changes of C_{Cr} and C_{PAH} during compensatory renal hypertrophy are adaptive, and the changes of Tm_{PAH} are growth dependent (2). We found that no matter how the compensatory renal hypertrophy is caused, the maximum ability to transport p-amino-hippuric acid is proportional to the tissue growth, whereas C_{Cr} and C_{PAH} per unit of renal tissue increase throughout the studies. Adaptive changes may be caused by the increased workload. Furthermore C_{Cr} or C_{IN} and C_{PAH} have been determined several times to be about 60 to 70% of the function of two kidneys immediately after unilateral nephrectomy (11, 16, 17). This can be explained by the fact that all nephrons are not perfused at any one time. In microscopic examinations Milovidow (1940) found 40% to 80% of active glomeruli in the remaining dog kidney immediately following unilateral nephrectomy, whereas the percentage was found to be 20% to 40% in the removed kidney (9). This has been confirmed in rats by Hartman and Bonfilio (1959) (6). Elias, Hossmann, Barth and Solmor (1960) found, by transillumination studies of the normal frog kidney, that there is a continuous shift in blood flow through different glomeruli (4). Morrison and Howard (1966) found that a 5/6 nephrectomy in rats was followed by a considerable greater C_{IN} per nephron (as determined by glomerular counts) than in sham-operated rats (10).

Accepting Bricker's intact nephron hypothesis we could rename Hinman's renal counterbalance theory as 'nephron counterbalance'. (7). Nephron counterbalance would indicate that identical hypertrophy and hyperfunction will take place in residual nephrons of the chronically diseased kidney and of the contralateral normal one. This study does not prove this, but microdissection studies in pyelonephritic kidneys (15) and hydronephrotic kidneys (1) show, that hypertrophy takes place in residual nephrons of diseased kidneys. An equivalent hyperfunction seems obvious, but it is difficult to investigate, and so far no such information is available.

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