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# RENAL FUNCTIONAL OUTCOME IN UNILATERAL HYDRONEPHROSIS IN NEWBORN PIGS

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## ABSTRACT

Purpose: We followed the course of neonatally induced, partial unilateral ureteral obstruction in pigs and established whether early function or morphological evaluation of the hydronephrotic kidney is predictive of outcome.

Materials and Methods: In 25 piglets unilateral partial ureteropelvic obstruction was induced 2 days after birth, while 11 underwent sham operation. Only obstructed kidneys with significant dilatation at 4 weeks were included for further study. Renal function was assessed on renography using $^{99m}$technetium-diaminetriaminepentaacetic acid differential uptake. According to the plasma clearance of $^{99m}$technetium-diaminetriaminepentaacetic acid the glomerular filtration rate was determined at ages 4, 12 and 24 weeks. Kidney morphology was studied in parallel by magnetic resonance imaging.

Results: A total of 12 obstructed kidneys with grade 3 or 4 hydronephrosis fulfilled study inclusion criteria. Of 6 kidneys with a functional share of 40% or greater at age 4 weeks 2 deteriorated to less than 40% at 24 weeks, while 4 of 6 with a share of less than 40% at age 4 weeks improved to greater than 40% at 24 weeks. The single kidney glomerular filtration rate at 4 weeks did not correlate with that at 12 or 24 weeks but the rate at 12 weeks correlated with that at 24 weeks ($r^2 = 0.8140$, $p < 0.001$). Neither relative volume of the obstructed kidney nor length of the contralateral nonobstructed kidney correlated with functional share of the obstructed kidney at any age.

Conclusions: Early evaluation of kidney function or volume, or contralateral kidney length did not predict the outcome of neonatally induced unilateral hydronephrosis in pigs.

KEY WORDS: hydronephrosis, kidney, ureteral obstruction, swine, forecasting

Prenatal ultrasound identifies a large population of asymptomatic children with congenital dilatation of the upper urinary tract. A recent study showed that only a minor fraction of these cases involve obstruction when defined as a decrease in function with time.[1] However, to our knowledge there are currently no exact methods to determine whether function of a hydronephrotic kidney would or would not deteriorate. The routine methods of predicting whether a hydronephrotic kidney would be functionally compromised are pelvic and caliceal dimensions,[2,3] the Whitaker test,[4] differential uptake on renography,[2,5,6] drainage curve patterns and prolonged half-time values on renography,[7] and accelerated growth of contralateral kidney length.[8,9]

Indications for surgical intervention are controversial. They have been set empirically at an initial renographic functional share of less than 30%,[7] 35%[10,11] or 40%.[5,6] Pelvic size is also used as an indication for surgery and early pyeloplasty was recommended by Dhillon when hydronephrosis exceeded 50 mm. in renal anteroposterior diameter.[2] Recently another approach was suggested based on the renal counterbalance phenomenon described by Hinman more than 75 years ago.[12] Briefly, Koff et al proposed that deterioration should be assessed by measuring changes in length of the contralateral kidney.[8]

We evaluated the development of kidney function and morphology in a morphologically well-defined model of induced dilatation with a close resemblance to that in children. We used a porcine model with polypapillary kidneys and predominately short looped nephrons similar to those of human kidneys.[13] Furthermore, in pig kidneys nephrons continue to form up to age 3 weeks.[14] Therefore, we considered that obstruction induced at age 2 days would mimic late prenatal obstruction in human fetuses. The animals in our study were followed until age 24 weeks, corresponding to early human adolescence. Parameters normally used for the clinical assessment of congenital unilateral hydronephrosis were applied to describe and when possible predict the course and outcome.

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## MATERIALS AND METHODS

Included in our study were 36 female Danish Landrace piglets weighing between 1.10 and 2.25 kg. in which obstruction was induced at day 2 of life. Preoperatively all animals underwent magnetic resonance imaging (MRI) to exclude those with visible signs of congenital abnormalities of the kidneys and urinary tract. None of the animals had any visible abnormality. The study complied with the Danish regulations for care and use of experimental animals.

Piglets were pre-anesthetized using midazolam and azaperonum, and intravenous access was established. They were subsequently intubated and ventilated with a gas mixture of oxygen and nitrous oxide at a ratio of 2:1. Anesthesia was maintained with 1.2% isoflurane. Using sterile technique a 2.5 to 3 cm. flank incision was made on the left side. The muscle layers were divided and the peritoneum was gently

pushed medial. A total of 11 and 25 piglets were then randomized to sham operation and partial ureteral obstruction, respectively. Obstruction was created using the method of Ulm and Miller[15] by embedding the ureter in the psoas muscle. In the sham operated group the ureter was left nonimplanted outside the muscle. The abdominal muscular layers and skin were then closed.

Included in further study were only 12 of the 25 pigs with an obstructed kidney, in which MRI revealed pelvic ectasia at age 4 weeks. At ages 4, 12 and 24 weeks isotope evaluation and MRI were performed using a standard hydration regimen of 15 ml./kg. per hour of isotonic saline administered for 1 hour before evaluation and 10 ml./kg. per hour during the whole study. Subjects remained lightly sedated with ketamine and midazolam given intravenously. Intravenous access for blood sampling was obtained by inserting an indwelling intravenous 0.45 × 0.85 mm. or 18 gauge, 600 mm. double lumen catheter in a central vein via a superficial abdominal vein. A catheter was placed transurethrally in the bladder and urine was obtained for culture.

Kidney function was assessed using combined $\gamma$ camera renal scintigraphy and plasma clearance techniques in response to a bolus injection of 100 MBq. $^{99m}$technetium-diethylenetriaminepentaacetatic acid ($^{99m}$Tc-DTPA). Dynamic renal scintigraphy was performed using a $\gamma$ camera and an on-line computer. Regions of interest over the kidneys and background were defined, and time activity curves were generated. Functional share was calculated as the uptake ratio of each kidney during the second and third minutes of the background subtracted integral of a $^{99m}$Tc-DTPA dynamic time activity curve.

The glomerular filtration rate was calculated as the total plasma clearance of $^{99m}$Tc-DTPA based on 17, 0.7 ml. blood samples obtained during 240 minutes after injection. After each blood sample was obtained the catheter was flushed with 1 ml. saline. Samples were centrifuged and plasma was counted in a well crystal scintillation detector to a statistical accuracy of 1%. For calculating the area under the curve the detector was fitted with 3 exponential functions using the peeling off technique. Single kidney glomerular filtration rate was calculated using the formula, glomerular filtration rate × functional share of the left and right kidney, respectively.

At age 4 weeks the kidneys were divided into 2 groups depending on the fractional uptake of $^{99m}$Tc-DTPA and derived functional share. The 2 groups comprised kidneys with a functional share of 40% or greater and less than 40%, respectively, while the third group included kidneys from sham operated pigs.

Renal volume and length were measured by MRI. The pigs were placed supine in the 1.5 Tesla magnet. To cover each kidney we planned axial slices 3 mm. thick with interscan spacing 0 mm. and field of view 16 to 28 cm. depending on age. A 2-dimensional spin echo sequence with echo time 25 msec., repetition time 400 msec. and 256 × 192 was applied. After image reconstruction in the renal area the medulla and whole kidney were measured semiautomatically by 2 independent observers. Total kidney volume including the intrarenal pelvis is presented as cm.$^3$/kg. body weight. Renal length estimated by measuring the kidney longitudinally from the upper to the lower pole is presented as cm./kg. body weight.

By calculating relative kidney volume each pig served as its own control for kidney size and, thereby, hydronephrosis. In accordance with Society for Fetal Urology recommendations the extrarenal pelvis was not included in volume estimation since it is believed that a prominent extrarenal pelvis may be determined to be wide yet not reflect obstruction.[4] Hydronephrosis grade at 4 weeks was estimated using gadolinium-enhanced images according to Society for Fetal Urology guidelines.[16] In grade 3 hydronephrosis all calices are visualized, while grade 4 hydronephrosis represents grade 3 with parenchymal thinning.

Renal length and volume are presented as the average of 3 independent measurements obtained by 2 individual investigators. Relative volume was calculated for each obstructed or sham operated kidney using the formula (left kidney volume/volume of left kidney + volume of right kidney) x 100. Intra-observer and interobserver variance was calculated for kidney length at ages 4, 12 and 24 weeks, and presented as the mean difference plus or minus standard error of mean (SEM) as well as mean observer difference in the percent of mean kidney length separately per age.

Body weight, functional share, glomerular filtration rate, single kidney glomerular filtration rate, relative kidney volume and renal length are expressed as the mean plus or minus SEM/kg. body weight. Body weight, functional share, glomerular filtration rate, single kidney glomerular filtration rate, relative kidney volume and renal length were tested for normalcy and compared using 1-way analysis of variance with $p < 0.05$ considered statistically significant. Correlations of the single kidney glomerular filtration rate at various ages, functional share, and kidney volume and length were analyzed by linear regression.

## RESULTS

MRI revealed normal appearing kidneys in all pigs in our study before obstruction was induced. A total of 12 animals fulfilled our study criteria at age 4 weeks with grade 3 or 4 hydronephrosis on gadolinium enhanced MRI (fig. 1). One animal with obstruction that died of cardiac arrest while under anesthesia during the 24-week evaluation investigation is included in the study at ages 4 and 12 weeks. Except for 1 positive culture in a sham operated pig no urinary tract infections were detected at any time in any animal during the study period.

Body weight did not differ significantly in obstructed and sham operated pigs during the study. At ages 2 days, and 4,

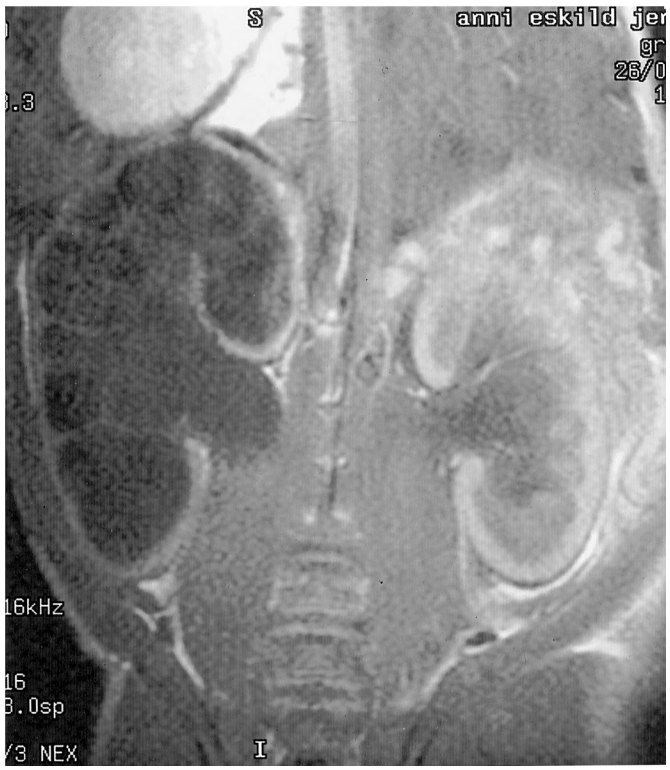


FIG. 1. Representative MRI of hydronephrotic kidney at age 4 weeks.

12 and 24 weeks mean body weight was 1.79 ± 0.07 kg. versus 1.78 ± 0.08 ($p = 0.93$), 3.93 ± 0.23 versus 4.19 ± 0.42 ($p = 0.58$), 21.4 ± 1.27 versus 24.3 ± 3.10 ($p = 0.34$) and 37.2 ± 1.83 versus 39.8 ± 4.02 ($p = 0.54$), respectively. At 4 weeks average renal functional share in the obstructed group was significantly decreased compared to that in the sham operated group (39% ± 4% versus 50% ± 1%, $p = 0.01$). At 12 and 24 weeks functional share of the obstructed and sham operated kidneys did not differ significantly (43% ± 3% versus 50% ± 1%, $p = 0.05$ and 43% ± 4% versus 49% ± 2%, $p = 0.15$, respectively). No significant difference was observed in functional share of obstructed kidneys at ages 4, 12 and 24 weeks ($p = 0.65$).

Figure 2 shows the functional share of all obstructed kidneys and the average in sham operated kidneys at ages 4, 12 and 24 weeks. Of the 6 obstructed kidneys with a functional share of 40% or greater at 4 weeks 2 deteriorated from 44% and 40% at 4 weeks to 26% and 34% at 12 weeks, further decreasing at 24 weeks to 17% and 22%, respectively (fig. 2, *A*). In 1 obstructed kidney the functional share decreased from 49% at 4 weeks to 43% at 24 weeks, while in the remaining 3 in this group it was stable. Of the 6 obstructed kidneys with an initial functional share of less than 40% 4 improved to greater than 40% at 12 and 24 weeks (fig. 2, *B*), 1 deteriorated from 39% at 4 weeks to 35% at 12 and 32% at 24 weeks, and 1 was lost before the 24-week evaluation but function improved from 7% at 4 weeks to 31% at 12 weeks.

At age 4 weeks the mean single kidney glomerular filtration rate was significantly decreased in obstructed versus sham operated kidneys (1.07 ± 0.13 versus 1.73 ± 0.14 ml. per minute per kg., $p < 0.01$). At 12 and 24 weeks the mean single kidney glomerular filtration rate did not differ in obstructed and sham operated kidneys (1.27 ± 0.12 versus 1.30 ± 0.12 ml. per minute per kg., $p = 0.85$ and 0.76 ± 0.08 versus 0.85 ± 0.07, $p = 0.41$, respectively). The mean single kidney glomerular filtration rate in obstructed pigs at 4 weeks did not correlate with that at 12 or 24 weeks ($r^2 = 0.1201$, $p = 0.26$ and $r^2 = 0.0005$, $p = 0.99$, respectively, fig. 3, *A* and *B*). However, the mean single kidney glomerular filtration rate at 12 weeks correlated with that at 24 weeks ($r^2 = 0.8140$, $p < 0.001$, fig. 3, *C*). This finding suggests that function at age 12 weeks predicts function at 24 weeks. Mean relative volume of the obstructed kidneys was significantly higher than that of sham operated kidneys at 4, 12 and 24 weeks (65.1% ± 1.8% versus 48.1% ± 2.3%, $p < 0.0001$; 63.5% ± 3.0% versus 52.8% ± 0.8%, $p < 0.01$, and 60.5% ± 3.5% versus 51.6% ± 0.5%, $p = 0.03$, respectively). Relative kidney volume did not correlate with functional share at 4, 12 or 24 weeks ($r^2 = 0.1814$, $p = 0.19$; $r^2 = 0.1203$, $p = 0.30$, and $r^2 = 0.4703$, $p = 0.02$, respectively).

Figure 4 shows the individual course of the relative volume of obstructed kidneys with an initial functional share of 40% or greater and less than 40% at 4 weeks, respectively. The course and value of relative kidney volume did not correlate with the initial functional share or functional course of obstructed kidneys. The 2 obstructed kidneys with an initial functional share of 40% or greater that decreased to less than 40% were no different from those in which it remained greater than 40% (fig. 4, *A*). The single obstructed kidney with an initial functional share of less than 40% that did not improve to greater than 40% had a large relative volume at all ages but we noted no clear difference from kidneys that improved to 40% or greater (fig. 4, *B*).

We also noted no difference in mean length of kidneys contralateral to the obstructed and control kidneys at 4, 12 and 24 weeks (1.65 ± 0.09 cm./kg. versus 1.57 ± 0.14, $p = 0.61$, 0.44 ± 0.02 versus 0.42 ± 0.03, $p = 0.53$ and 0.28 ± 0.01 versus 0.26 ± 0.02, $p = 0.42$, respectively). To determine whether changes in the functional share of obstructed kidneys were associated with the length of the contralateral nonobstructed kidney we compared these 2 parameters. Mean length of the contralateral kidney did not correlate with functional share of the obstructed kidney at 4, 12 or 24 weeks ($r^2 = 0.2145$, $p = 0.13$; $r^2 = 0.0781$, $p = 0.38$ and $r^2 = 0.0459$, $p = 0.53$, respectively). Mean image modality intraobserver variance was 0.25 ± 0.08 cm. or 2.4% of mean kidney length at 4 weeks, 0.22 ± 0.04 cm. or 2.2% at 12 weeks and 0.16 ± 0.02 cm. or 2.4% at 24 weeks. Mean interobserver variance was 0.31 ± 0.08 cm. or 2.9% of mean kidney length at 4 weeks, 0.29 ± 0.05 cm. or 2.9% at 12 weeks and 0.17 ± 0.02 cm. or 2.6% at 24 weeks.

## DISCUSSION

The major findings in our study were that the individual functional course of obstructed kidneys was not predicted by early renographic evaluation, the initial single kidney glomerular filtration rate, relative kidney volume or length of the contralateral nonobstructed kidney. We noted no correlation of relative kidney volume or contralateral kidney length with functional share at any age. Determining renal function in early life does not predict functional development. Functional share is considered by some to be a decisive factor in the appropriate management of unilateral hydronephrosis.[3, 5–7, 10, 11] The threshold for surgical intervention is arbitrarily chosen at a functional share of less than 30% to 40%. Therefore, we categorized obstructed kidneys with grade 3 or 4 hydronephrosis into 2 groups based on a functional share of 40% or greater and less than 40% on renography at age 4 weeks. Of the 6 obstructed kidneys with an initial functional share of less than 40% 4 improved to normal at 12 and were

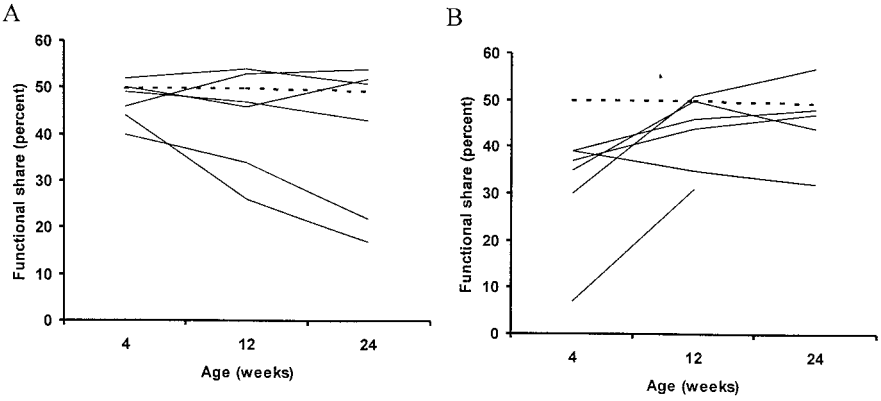


FIG. 2. Functional share of obstructed (solid lines) and average share of sham operated (broken lines) kidneys at age 4 versus 4, 12 and 24 weeks. *A*, 40% or greater. *B*, less than 40%.

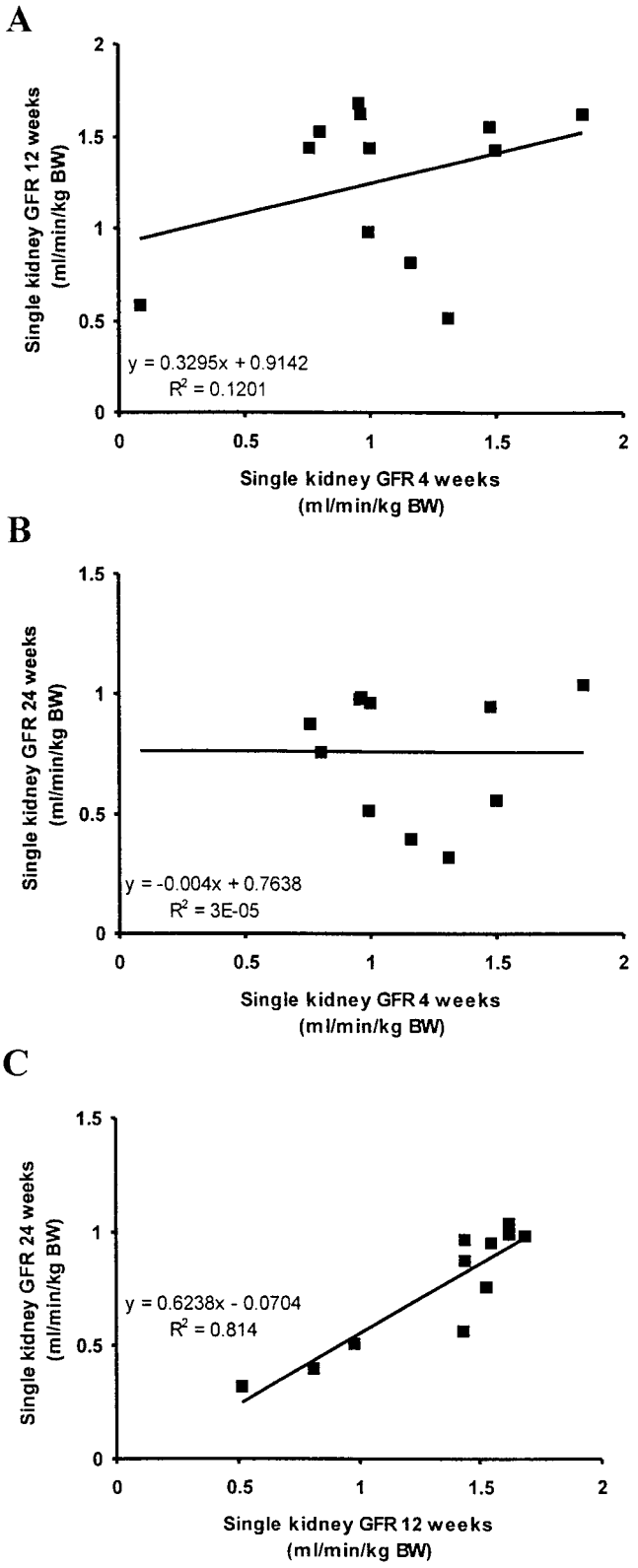


FIG. 3. Glomerular filtration rate (*GFR*) of single obstructed kidneys. *A*, at age 4 versus 12 weeks. *B*, at 4 versus 24 weeks. *C*, at 12 versus 24 weeks. *BW*, body weight.

stable at 24 weeks, while 2 of the 6 obstructed kidneys with a share of greater than 40% deteriorated to less than 40%.

To our knowledge few clinical studies describe the natural history of this condition. Except for the series of Koff et al[17, 18] most exclusively involve kidneys with an initial functional share of greater than 35% to 40%. Our study supports the finding that early functional share does not predict functional outcome. Koff and Campbell,[17] and Ulman et al[18] nonoperatively followed 104 neonates with congenital grade 3 or 4 hydronephrosis regardless of the initial functional share. During a mean followup of 6.5 years 22% of patients had a deteriorating functional share and/or increasing hydronephrosis, which was an indication for surgical intervention. Koff and Campbell noted an initial functional share of 40% or less in 16 kidneys, including 1 in which functional share deteriorated and 14 in which it improved to greater than 40% during a mean followup of 21 months.[17] Deteriorating renal function was observed in 6 of 39 kidneys with an initial functional share of greater than 35% by Cartwright et al during a mean followup of 18 months[10] and in 14 of 100 with an initial share of greater than 40% by Ransley et al during a mean followup of 1 to 6 years.[6] However, these studies were of shorter duration than ours and longer followup may detect more deteriorating kidneys.

In our study functional share stabilized from ages 12 to 24 weeks, although in the 2 kidneys with deteriorating function the share decreased further, indicating that after the initial unstable phase a state of equilibrium is generally achieved. This observation is supported by Ulman et al, who performed pyeloplasty due to decreasing function or increasing hydronephrosis within the initial 14 months of life.[19] In other studies the majority of pyeloplasties were performed within the initial 3 years of life.[2, 6] However, to our knowledge no group followed children long enough to document whether nonoperated kidneys remain stable. In our study the pigs were followed until age 24 weeks, corresponding to early adulthood in humans.

To distinguish children who would benefit from surgery from those in whom dilatation is inconsequential Dhillon suggested pelvic size as a predictor of functional outcome.[2] In our study total kidney volume, including that of the intrarenal pelvis, was used to describe the degree of hydronephrosis. The ideal parameter may have been a measure of the pelvis or parenchyma. Unfortunately we realized during analysis that intrarenal structures with a high water content, such as papillae and possibly part of the inner medulla, were not reliably distinguished from the pelvis by noncontrast enhanced MRI. Therefore, we substituted a pelvic estimate with a measure of the whole kidney, including the intrarenal pelvis.

In our long-term study there was a tendency toward an association of a large intrarenal pelvis expressed as a large obstructed kidney and a low functional share at all ages. However, a large kidney did not correlate with decreased function or later functional outcome. As in our study, Josephson did not note any correlation of functional impairment with degree of pelvic enlargement in neonatal obstructed rat kidneys.[19] Our results are also supported by those of Takla et al,[11] and Freedman and Rickwood[5] who observed no correlation of initial postnatal hydronephrosis grade with the likelihood of surgical resolution, as indicated by impaired renal function or drainage, or the incidence of impaired renal function, respectively, in patients with prenatally diagnosed hydronephrosis. However, our findings contradict the observations of Dhillon, who followed 36 children with initially good hydronephrotic kidney function.[2] Seven kidneys had decreasing function after 1 year of observation and all had a minimum of 20 mm. of initial dilatation. However, overall mean pelvic diameter was 23 mm. (range 15 to 50) and 9 of 17 children in whom dilatation improved spontaneously also had initial dilatation greater than 20 mm.

Serial measurements of the length of the contralateral nonobstructed kidney were suggested by Koff et al as a diagnostic test for obstruction in cases of unilateral hydronephrosis.[8] In children Koff et al noted that kidneys contralateral to hydronephrotic kidneys with a decreasing functional share had accelerated length growth and were significantly longer

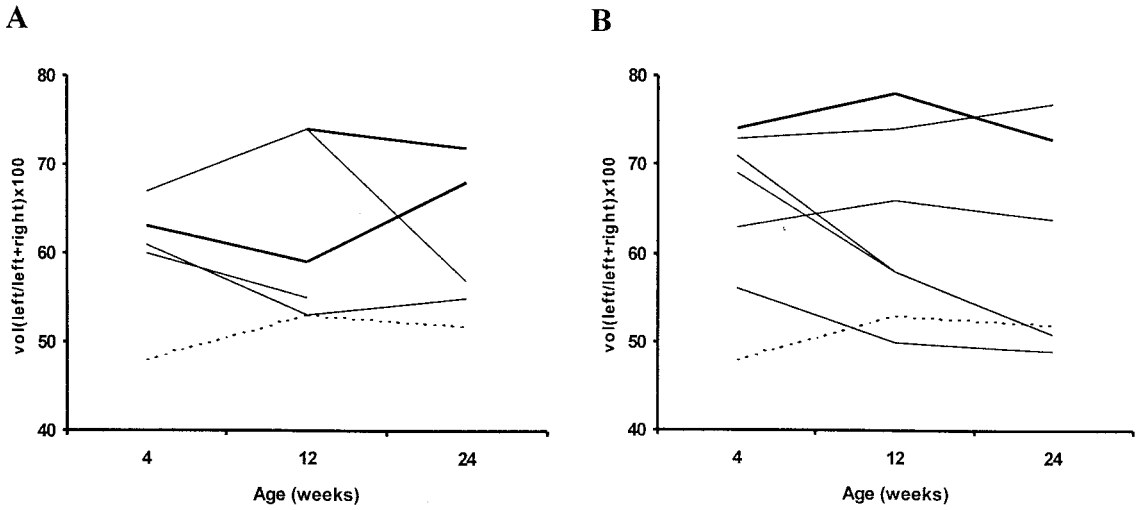


FIG. 4. Relative volume of obstructed kidneys (solid lines) and average volume of sham operated kidneys (dashed line) at 4, 12 and 24 weeks. *A*, functional share 40% or greater. Bold lines represent 2 obstructed kidneys with initial 40% or greater functional share at 4 weeks that decreased to less than 40%. *B*, functional share less than 40%. Bold line represents 1 obstructed kidney that did not improve to greater than 40% functional share.

than normal for age, whereas those contralateral to hydronephrotic kidneys with an increasing functional share had a decreased length growth rate. We observed no association of length of the contralateral nonobstructed kidney with functional share of the obstructed kidney at any age. These findings confirm those of Brandell et al, who in a retrospective study detected no correlation of single measurements of renal length with the presence or absence of obstruction in hydronephrotic kidneys judged by furosemide renography and hydronephrosis grade.[9]

## CONCLUSIONS

Our study shows that the early measurement of functional share, single kidney glomerular filtration rate, volume of the obstructed kidney or length of the contralateral nonobstructed kidney in our model did not differentiate kidneys with later decreasing function from those with insignificant hydronephrosis. After the initial phase renal function stabilizes compared with that in sham operated kidneys regardless of the initial functional level, although kidneys with decreasing function deteriorate further.

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