Urol Res (1996) 24:161–166

ORIGINAL PAPER

K. J. A. Kairemo · K. Taari · J. O. Salo · A. Kivisaari
S. Rannikko

Renal function remains after unilateral total and contralateral partial nephrectomy: an experimental study in pigs using ^{99m}Tc-DTPA

Received: 12 October 1995 / Accepted: 5 February 1996

Abstract Twelve nephrectomies (NEs) were performed in 12 pigs (11–17 kg). Total NE was performed on the left side and partial NE on the right side (lower third of the kidney), thus two-thirds of the total kidney volume was removed. Renal function was studied with ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) renography and serum urea and creatinine levels preoperatively, and 1 and 2 weeks postoperatively. The pigs were imaged in each session for 30 min by collecting 10-s frames from a posteroanterior (PA) view of an anaesthesized animal. The injected activity was 37 MBq. Serial blood samples were taken from the subclavian vein at 0, 1, 2, 3, 5, 15, 25, 40, 60 and 120 min (six animals) after ^{99m}Tc-DTPA injection. The DTPA disappearance rate (DDR) was determined from these samples and in other cases (six animals) a blood sample at 20 min was used. The DDR was also determined from the dynamic gamma imaging data: Regions of interest (ROI) were upper body, spleen, heart and kidneys. The ROI analysis correlated well with the blood sampling data ($r = 0.97$, $P < 0.0001$). The reference values for pig DDRs were 0.99 $\pm$0.08%/min. These values were 0.71 $\pm$ 0.08%/min at 1 week postoperatively and 0.63 $\pm$ 0.08%/min at 2 weeks. DTPA clearance rates were preoperatively 0.53 $\pm$0.06 ml/s; at 1 week postoperatively 0.41 $\pm$ 0.06 ml/s; and at 2 weeks 0.35 $\pm$ 0.06 ml/s. There were no significant differences pre- and postoperatively in creatinine and urea concentrations. The DTPA clearance (ml/s) and disappearance rates (%/min) when determined per kidney area (cm^2) increased significantly ($P < 0.001$ at both 1 and 2 weeks); in 11 of 12 animals the function of the resected right kidney was higher than the split function of the whole right kidney preoperatively. Unilateral nephrectomy initiates a functional adaptation or a growth response in the contralateral kidney to compensate for the loss of a renal mass. These data also indicate that two-thirds of the kidney volume in young pigs can be removed without danger.

Key words Partial nephrectomy · Kidney function · Renography · Radionuclide imaging · ^{99m}Tc-DTPA

K. J. A. Kairemo (✉)
Department of Clinical Chemistry,
Helsinki University Central Hospital, Haartmaninkatu 4,
FIN-00290 Helsinki, Finland

K. Taari · J. O. Salo · S. Rannikko
Department of Urology, Helsinki University Central Hospital,
Helsinki, Finland

A. Kivisaari
Department of Radiology, Helsinki Central Hosptial, Helsinki,
Finland

Introduction

The standard therapy for localized renal cell cancer is nephrectomy. The use of partial nephrectomy or kidney resection in the treatment of renal malignancies is increasing because small incidental carcinomas are found more often on non-invasive imaging examinations, and the long-term survival results of parenchyma-conserving surgery are favourable [8].

Unilateral nephrectomy initiates a growth response in the contralateral kidney to compensate for the loss of a renal mass. In a study with two groups of rabbits (1.5–2 months and 2 years of age) after unilateral nephrectomy in both young and old age groups, the kidney weight increased by 119% and 38%, the ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) glomerular filtration rate (GFR) by 71% and 44%, and the ^{99m}Tc-DTPA effective renal plasma flow (ERPF) by 116% and 35% [1]. Thus, nephrectomy in younger animals when kidneys grow rapidly leads to much better compensatory hypertrophy in the remaining kidney than at old age.

The kidney function using the ^{99m}Tc-DTPA test after nephrectomy has been studied experimentally in pigs [14–16, 18, 22], dogs [2], rabbits [6] and rats [4]. Robbins et al. [14] studied pigs aged approximately 10 months after single intravenous doses of 1.5, 2 or 2.5 mg/kg cisplatin and unilateral nephrectomy; cisplatin treatment was associated with a marked reduction in the ability of the remaining kidney to increase its function in terms of GFR and, to a lesser extent, of ERPF, being only 50%–70% of that seen in age-matched nephrectomized controls [16]. Their group has also studied younger pigs, approximately 14 weeks of age, which were irradiated with single doses of 7–12.6 Gy 250-kV X-rays, and kidneys receiving 8.8 Gy were assessed as having no significant function. Four weeks after unilateral nephrectomy at the age of 10 months there was a pronounced increase in GFR and, in particular, ERPF in previously irradiated kidneys with no function (> 8.8 Gy) [14]. Worthley et al. [22] conducted 19 pairs of GFR estimations in 10 pigs: 7 in normal pigs and 12 following bile duct ligation and/or nephrectomy, finding that absolute and weight-normalized endogenous creatinine clearances correlated significantly with ^{99m}Tc-DTPA elimination. Hagemann et al. [4] performed unilateral nephrectomy in 109 male Wistar rats, with 35 animals as controls. Determinations of glomerular filtration rate (GFR) using slope clearance of ^{99m}Tc-DTPA were performed 2 and 5 days as well as 2, 4, 5 and 6 weeks after nephrectomy. In all examinations the GFR was more than 50% of the level of two-kidney control animals. Fractional maximum diuresis was increased in the first two examinations after nephrectomy from $8.9 \pm 2.1\%$ to $15.4 \pm 4.2\%$ of the GFR. These experimental data verify that ^{99m}Tc-DTPA renography can be used to assess GFR and ERPF after nephrectomy and the split function for single kidneys can be reliably determined. However, it is not known whether ^{99m}Tc-DTPA disappearance rate can be used to assess DTPA clearance, whether it correlates with DTPA elimination from blood and what the reference values are for pigs. It is not known how these parameters are affected by nephrectomy.

Therefore, we studied 12 pigs 3 times (in total 12 preoperative and 24 postoperative renographies) after total (left kidney) and partial nephrectomy (right kidney). The specific aims of the study were: (1) to calculate reference values of ^{99m}Tc-DTPA clearance and ^{99m}Tc-DTPA disappearance rate for pigs, (2) to study the effect of the decreased total kidney volume on the functional kidney capacity and (3) to study postoperative recovery after total and partial nephrectomy.

Materials and methods

Animals

Twelve Finnish native pigs, 1.5–3 months of age (mean weight 14 kg, range 11–17 kg), were used.

Surgery

We have previously reported a comparison of the Nd-YAG laser and the steel scalpel for partial nephrectomy; the present study was a part of this project, which has been published elsewhere [19, 20]. Briefly, 12 partial nephrectomies were performed in 12 pigs using either the combination (contact and non-contact) Nd-YAG laser technique or the steel scalpel. Lower pole guillotine resection was performed at the junction of the mid and lower thirds of the right kidney (six resections with the laser scalpel, six with the steel scalpel). The renal artery was not clamped and renal cooling was not attempted. Total nephrectomy was performed on the left side.

Laboratory examinations

Serum creatinine and urea levels were measured preoperatively and 1 and 2 weeks postoperatively.

Renography

A total of 37 MBq ^{99m}Tc-DTPA (Solco-DTPA, Solco, Basel, Switzerland) was injected intravenously into the subclavian vein of an anaesthesized pig. The 30-min imaging was performed using a Siemens Rota gamma camera by collecting 10 s/frame. A low-energy high-resolution collimator was used and the matrix size was $128 \times 128 \times 16$. The gamma camera was connected to a PDP-11 computer utilizing Gamma-11/40 software. Activity distribution on gamma images was analysed by the region of interest (ROI) method [21]: upper body, spleen (background), heart and kidney were drawn to obtain dynamic nephrograms and to calculate ^{99m}Tc-DTPA disappearance rate as %/min. A blood sample from the subclavian artery was taken at 20 min to convert the ^{99m}Tc-DTPA clearance to ml/s. The gamma images were analysed by a nuclear physician (K.J.A.K.) with no knowledge of the operative history of the pig. Serial blood samples were taken from the subclavian artery of six animals at 1, 2, 3, 5, 15, 25, 40, 60 and 120 min to measure the absolute ^{99m}Tc-DTPA. These blood samples of 1.0 ml were measured using a gamma counter (LKB 1282, Wallac Oy, Turku, Finland) against a known standard reference activity.

Urography

Intravenous urography with iohexol 450 mg iodine/kg (Omnipaque, Nycomed, Oslo, Norway) was performed preoperatively and 2 weeks postoperatively. Kidney area was measured on plain X-ray films by a radiologist (A.K.), with no knowledge of the operative history of the animal.

Results

The ^{99m}Tc-DTPA elimination rate calculated from the blood samples of six pigs in three imaging sessions correlated well with DTPA disappearance rate calculated from dynamic gamma imaging data ($r = 0.97$, $P < 0.0001$).

The average DTPA disappearance rate and DTPA clearance in all imaging sessions are shown in Table 1. The reference values for healthy pigs were 0.99 $\pm$ 0.20%/min (mean $\pm$ SEM) for DTPA disappearance

Table 1 Serum creatinine and urea values, DTPA disappearance and DTPA clearance rates preoperatively and 1 and 2 weeks postoperatively (means ± SEM)

	Pre-operative	1 week postoperatively	2 weeks postoperatvely
Creatinine (µmol/l)	90 ± 5	119 ± 5	116 ± 6
Urea (mmol/l)	2.8 ± 0.4	3.7 ± 0.5	3.6 ± 0.4
DTPA disappearance rate (%/min)	0.99 ± 0.08	0.71 ± 0.08	0.63 ± 0.08
DTPA clearance rate (ml/s)	0.53 ± 0.06	0.41 ± 0.06	0.35 ± 0.06

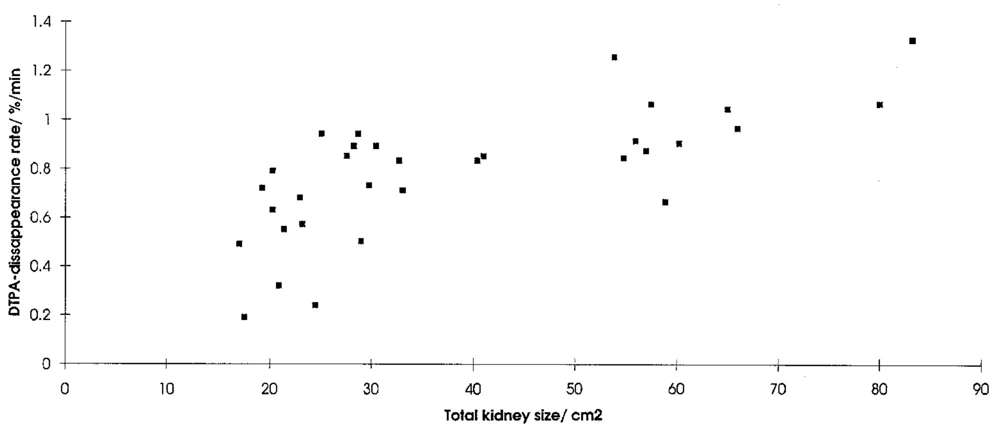

Fig. 1 Correlation between total kidney size and DTPA disappearance rate ($r = 0.36$, $P < 0.05$)

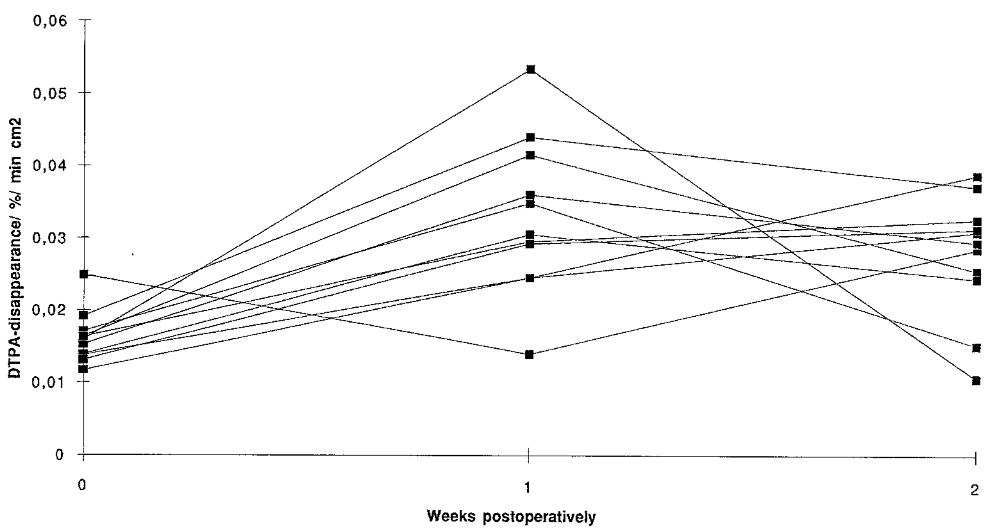

Fig. 2 Relative DTPA disappearance rate (DTPA disappearance rate/right kidney area) preoperatively and 1 and 2 weeks postoperatively. The DTPA disappearance rate increased between preoperative and postoperative measurements significantly [at 1 week ($P < 0.001$) and at 2 weeks ($P < 0.001$)]

rate and 0.53 ± 0.15 ml/s for DTPA clearance, respectively. The overall kidney function tends to decrease when only one-third of the kidney volume is left. The postoperative kidney function values are acceptable and most of them are within the reference limits of healthy animals. The serum creatinine and urea values demonstrate a slight tendency to increase (Table 1).

The total kidney size as measured from X-ray films varied from 16.2 cm^2 to 83.7 cm^2. There was a weak correlation between total kidney size and DTPA disappearance rate ($r = 0.36$, $P < 0.05$) (Fig. 1), but there was no correlation between single kidney area and DTPA disappearance rate ($r = 0.076$, NS). The right kidney split function and the function of the resected right kidney remained after total nephrectomy in individual animals – higher values in all animals except one (at 1 week) were measured postoperatively. When the relative DTPA disappearance rate (DTPA disappearance rate/kidney area) was calculated individually, higher values were obtained in 10 of 11 animals at 1 week and in 9 of 11 animals at 2 weeks postoperatively (Fig. 2). The mean values for the relative DTPA disappearance rates were 0.0148 ± 0.0026%/min cm^2 preoperatively, 0.0330 ± 0.0082%/min cm^2 1 week and 0.0260 ± 0.0068%/min cm^2 2 weeks postoperatively. The differences were significant between the relative DTPA disappearance rates pre- and postoperatively: at 1 week ($t = 4.91$, $P < 0.001$; two-tailed t-test) and at 2 weeks ($t = 4.19$,

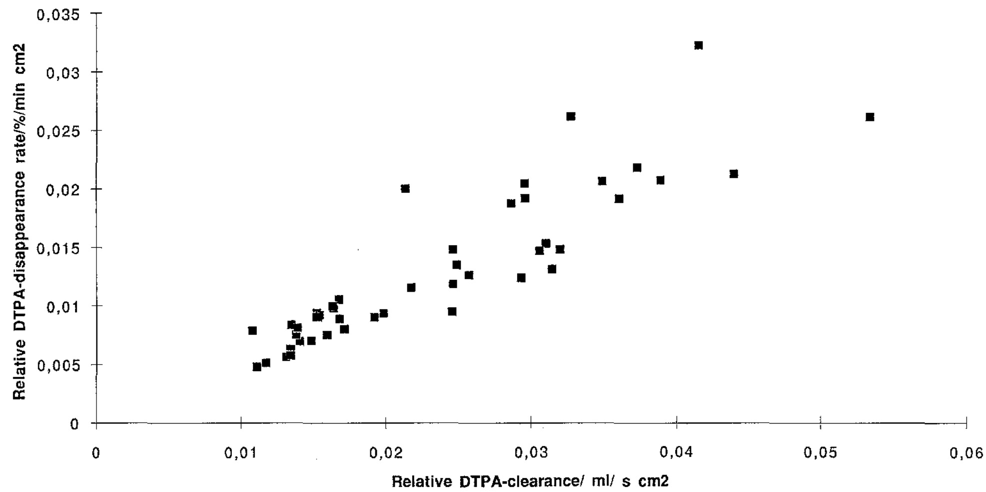

Fig. 3 Correlation between relative DTPA clearance (DTPA clearance/kidney area) and relative DTPA disappearance rate (DTPA disappearance rate/kidney area) ($r = 0.891$, $P < 0.0001$)

$P < 0.001$; two-tailed t-test). There was a strong correlation between the relative DTPA clearance and the relative DTPA disappearance rate ($r = 0.891$, $P < 0.0001$) (Fig. 3).

The kidney size was also measured by using ROI analysis on gamma images and there was no correlation between the kidney size on gamma image and X-ray film ($r = 0.064$, NS). Because no knowledge of the operative history was available at the time of analysis of gamma images, no phantom kidneys were observed.

Discussion

We have previously reported that there was no difference between the surgical procedures and their impact on the kidney function and postoperative recovery [18]. In this study we found that the overall kidney function tends to decrease when only one-third of the kidney volume is left. The reference values used for humans at our institution are >1.00%/min for DTPA disappearance rate and >0.50 ml/s for DTPA clearance, which are close to those we obtained for pigs (0.99 ± 0.20%/min and 0.53 ± 0.15 ml/s, respectively).

The average serum creatinine and urea values increased slightly from 90 to 115 mol/l and from 2.7 to 3.5 mmol/l, respectively, when only one-third of the kidney volume was left. The increment, however, was much less than that which could be expected without any compensative effect of the remaining kidney tissue. The kidney function parameters from dynamic gamma imaging also did not decrease to the same extent as the kidney volume. This leads to the conclusion that after nephrectomy the remaining kidney tissue has to adjust to new conditions. The capacity of the right kidney (partly resected) increased as a function of size in 10 of 11 animals at 1 week and in 9 of 11 animals at 2 weeks postoperatively. Nevertheless, the relative kidney function values were at least in one imaging session higher in all animals postoperatively.

Compensatory renal hypertrophy is the term applied to enlargement of the remaining renal mass that occurs after nephron ablation or reduction in functioning renal mass induced by various disease processes [7]. The degree of compensatory renal hypertrophy is greater the younger the age at which damage occurs [1, 7]. In children it has been shown that compensatory hypertrophy is proportional to the amount of contralateral cell damage [11].

The animals in the present study were quite young (1.5–3 months of age) and two-thirds of their kidney volume could be removed without danger. However, the follow-up time was only 2 weeks, and it is possible that the kidney function could deteriorate further after longer follow-up. Nevertheless, in the study by Hagemann et al. [4], there was no difference in ^{99m}Tc-DTPA glomerular filtration rate between 2 weeks and 4–6 weeks after nephrectomy in rats. A longer follow-up period in young pigs may also be more affected by normal growth. The mechanisms underlying compensatory renal hypertrophy are poorly understood [7]. Kidney-specific growth factors or renotropins have not been isolated. An alternative hypothesis is that local factors (e.g. increase in GFR) could trigger a series of events that sensitizes the kidney to normally existing growth factors [7].

We also found the glomerular filtration tracer ^{99m}Tc-DTPA useful for assessing DTPA clearance and disappearance rate: These entities are dependent on each other and they are both good markers for kidney function. They are not dependent on the kidney size as calculated for one kidney. These parameters can also be used to characterize the split function of a single kidney. Moonen et al. [10] studied the split renal function in 38 patients with kidney tumours prior to nephrectomy and in 32 control patients. They investigated the single kidney glomerular filtration rate using the integral, the slope and the uptake index methods for ^{99m}Tc-DTPA and ^{51}Cr-EDTA clearance. The reproducibility in calculating the relative renal function was very good with all three gamma imaging methods (coefficient of variation 2–4%) as compared to ^{51}Cr-EDTA clearance [10].

In another study the single kidney glomerular filtration rate from the ^{99m}Tc-DTPA renogram obtained by gamma camera was calculated in 20 unilaterally nephrectomized patients [13]. The GFR values obtained from the renograms and from the estimated endogenous creatinine clearances according to serum creatinine concentration and a nomogram were both accurate, whereas GFR calculated from the plasma clearance of ^{51}Cr-EDTA overestimated the renal clearance of inulin on an average by 11.3%. The day-to-day variation of GFR estimated from the renograms in 24 patients (48 kidneys) with single kidney GFR values from 5 to 76 ml/min was 8.8% [13]. This variation among individuals in consecutive analyses was also observed in the present study, and within these limits was less than 10%.

Sesso et al. [17] evaluated the long-term residual renal function in 64 living related kidney donors. Overall mean serum creatinine concentration after kidney donation was increased compared to baseline values (1.13 mg/dl vs 0.92 mg/dl, respectively, $P < 0.001$). At the last follow-up visit, post-nephrectomy mean GFR values measured by ^{99m}Tc-DTPA, adjusted for body surface area, age at donation, baseline serum creatinine concentration and duration of follow-up, were significantly lower in women than in men (72.11 ml/min vs 87.17 ml/min, respectively, $P = 0.02$). Their results also indicated that following nephrectomy serum creatinine concentration increased significantly as a function of greater age at donation in women but not in men [17].

Usually after standard nephrectomy the functional capacity of the remaining kidney is enough to compensate for the loss of the total kidney volume. The creatinine and urea levels will usually remain within normal limits in otherwise healthy and young patients. However, with co-existing diseases (e.g. diabetes and arteriosclerosis) the renal function is lower [3], and temporary or permanent dialysis may be mandatory.

In a study of 39 nephrectomized patients who underwent routine radionuclide kidney studies including blood flow imaging at various periods postoperatively, perfusion of varying degree was demonstrated in the area of the nephrectomized kidney in 17 patients showing equal or less activity than the actual kidney [9]. This so-called phantom kidney was reproducible in the same patient and was found 4 weeks to 10 years after nephrectomy [9]. This phantom kidney phenomenon may besides nephrectomy be related to congenital absence of the kidney [5]. Some conditions can also make the renal perfusion on a ^{99m}Tc-DTPA radionuclide study completely absent [12]. These phenomena must be borne in mind when interpreting dynamic gamma images in nephrectomized objects. We observed no phantom kidneys despite a great number of analyses in nephrectomized animals. Nor did we observe any other perfusion abnormalities.

In conclusion, unilateral nephrectomy initiates a functional adaptation or a growth response in the remaining kidney to compensate for the loss of the renal mass. The functional reserve of healthy kidneys allows removal of two-thirds of the kidney in young pigs without danger.

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