Urol Res (2010) 38:51–56
DOI 10.1007/s00240-009-0234-0

ORIGINAL PAPER

Urinary obstruction depresses erythropoiesis which recovers after parenchyma-saving surgery but not SWL

Davor Eterović · Marijan Šitum · Ante Punda · Vinko Marković · Slaven Kokić

Received: 6 November 2008 / Accepted: 4 November 2009 / Published online: 1 December 2009

Abstract We tested the hypotheses that chronic human urinary obstruction impairs the renal regulation of the red blood cell (RBC) production and compared the chronic outcome of relief of obstruction between parenchyma-saving surgery and extracorporeal lithotripsy (SWL). We measured RBC count and serum erythropoietin (Epo) concentration before and 3 months after relief of urinary obstruction in 60 patients treated with pyelolithotomy, ureterolithotomy or ureteroscopy and in 62 patients treated with SWL. Compared with 333 healthy controls, at baseline, patients scheduled for parenchyma-saving surgery had lowered RBC count [9.9% (6.9–13.1); 95% confidence interval] in case of males and 17.7% (14.2–21.4) in case of females; minor depression in RBC count was also observed in female patients scheduled for SWL. Epo serum levels were mildly reduced in SWL patients and halved in parenchyma-saving surgery group. At 3 months following relief of obstruction in 50 operated patients without recurrent or residual stone, Epo levels almost doubled, becoming normal, while RBC count and haemoglobin concentration increased for 6.1% (3.8–8.8) and 8.8% (6.1–10.6). In contrast, in 49 SWL patients only minor, bidirectional responses to treatment were observed. We conclude that obstructive uropathy is associated with clinically relevant effects on erythropoiesis, which is reversed after relief of obstruction by parenchyma-saving surgery that saves the renal parenchyma.

Keywords Kidney stone · Renal obstruction · Lithotripsy · Epo · Anaemia

D. Eterović · A. Punda · V. Marković
Department of Nuclear Medicine,
University Hospital Split, Split, Croatia

D. Eterović (✉)
Department of Medical Physics, Medical Faculty,
University of Split, Šoltanska 2, 21000 Split, Croatia
e-mail: davor.eterovic@mefst.hr

M. Šitum
Department of Urology, University Hospital Split, Split, Croatia

S. Kokić
Department of Medicine, University Hospital Split, Split, Croatia

Introduction

The acute complications of extracorporeal lithotripsy with shock waves (SWL) are rare, but well recognized. However, it is still unresolved how successful termination of urinary obstruction by SWL ultimately affects the renal functions and its control mechanisms. The basic problem is that positive effects of relief of urinary obstruction cannot be resolved from eventual detrimental effects of imperfect focusing of shock waves. Previously this problem was not recognized and the post-treatment renal functions were simply compared with pretreatment values. This approach neglects the possibility that renal-obstruction lesions are reversible, so that after successful treatment an improvement in functions is expected, rather than restoration of baseline values. This explains why chronic SWL-related renal lesions were underestimated. The fact that after SWL, following acute depression, renal functions chronically return to baseline values was interpreted as absence of chronic lesions [1, 2]. Clearly the method without collateral renal parenchymal lesions would show the net effects of relief of urinary obstruction. By using the results of pyelolithotomy, we showed that the various indexes of obstructed kidney function fully recover, approaching the values on unobstructed site, while arterial blood pressure decreases at

3 months after relief of obstruction in great majority of patients with significant obstruction, hydronephrosis and even infection at baseline. In contrast, only restoration of pretreatment functions was observed in SWL patients, despite being less obstructed than the pyelolithotomy group [3, 4].

We now hypothesize that similar effects are present in case of renal control of erythropoiesis. Although anaemia in patients with chronic renal failure [5–10] and transient depression of erythropoietin (Epo) production during uretheral obliteration in animal model and in human hydronephrosis have been reported [11–18], nobody addressed the possibility that even partial urinary obstruction in humans may be associated with inadequate production of Epo. We expected to see a depressed red blood cell count (RBC) and Epo levels in patients with urinary stones, which should renormalize following relief of obstruction without collateral lesions to kidney.

Methods

Study design

We first wanted to see whether the patients with urinary stones had depressed haematological parameters. Therefore, we compared them at baseline with the group of gender-matched control persons. We also wanted to see whether the group scheduled for parenchyma-saving surgery, with greater obstruction and its functional sequelae at baseline, differed in this respect from SWL group. Therefore, the baseline comparisons were made between these three groups (parenchyma-saving surgery, SWL and controls), separately for men and women. In order to estimate the potential sampling bias, two groups of control persons were used: the hospital and outpatient controls. We next wanted to evaluate the chronic effects of the therapy for urolithiasis. However, most of uncomplicated renal stones smaller than 3 cm are treated with SWL and the operation is reserved mainly for cases that do not satisfy those criteria. Consequently, it was impossible to use the randomized controlled trial to compare these methods. Thus, neither of those two groups of obstructed patients should be regarded as a control or comparative group since they differed at baseline. The possible confounding effect of residual or recurrent stone on the study outcome was recognized. In order to avoid this potential problem, the parenchyma-saving surgery in patients without residual or recurrent stone at 3 months was a model of the chronic effects of relief of urinary obstruction. The time span of 3 months was considered enough to resolve the acute from chronic effects, yet not too long to include the effects of aging.

In short, this study is a combination of a cross-sectional comparison of patients with urinary stones with control persons without urinary obstruction and diseases known to affect the blood homeostasis and an uncontrolled interventional study, on two different groups of patients with urinary stones, treated with two different methods.

Patients and control persons

Consecutive series of patients with unilateral stone scheduled for pyelolithotomy, ureterolithotomy, ureteroscopy or SWL in the Department of Urology, Clinical Hospital Split, were considered eligible. Uncomplicated renal pelvic stones less than 3 cm in diameter were treated with SWL, otherwise pyelolithotomy, ureterolithotomy or ureteroscopy with extraction of calculi were applied. The recruitment started in May 2002 and terminated in February 2005, when the predefined samples were obtained, as dictated by power requirements and detailed later. The eligible patients were those not treated for hypertension or anaemia before entering the study. The eligible patients were instructed about the proposed investigation and those patients willing to participate signed the written informed consent. It was predefined that the recruited patients with recurrent or residual stone at 3 months and those treated for hypertension or anaemia after entering the study would be dropped from the analysis of the outcome measures. The hospital controls were patients scheduled for minor surgical treatments at the departments of urology or dermatology, while outpatient controls were persons undergoing regular yearly checkups; both without diseases known to affect the blood haematopoiesis. The serum Epo concentrations were determined only in a random sub-sample of 60 control persons.

Methods

An electromagnetic lithotripter with biplane fluoroscopy was used. The patient was given an analgetic and the lidocaine cream applied on skin. The generation of shock waves was synchronized with repolarization phase of the cardiac cycle and the last third of the expiration phase of the respiratory cycle. During pyelolithotomy or ureterolithotomy general anaesthesia was maintained by isoflurane. About 10 mL of peripheral blood was drawn in the morning hours from 8 to 9 after overnight fasting, the first time in the week preceding the stone removal and the second time at 3 months following the procedure. The samples were subsequently frozen to −60°C. Radioimmunoassay method was used to measure the serum Epo concentration (EPO-*Trac* RIA, Incstar Corporation, Stillwater, MN, USA) according to manufacturer's instructions. The red blood cell count, including reticulocyte count was determined by standard methods. Each patient was also followed clinically, and all relevant routine pretreatment and follow-up tests and events were recorded, including ultrasound, intravenous

urography (all patients) and dynamic renal scintigraphy (some patients).

Outcome measures

The primary outcome measure was the post-treatment change in Epo serum level. The changes in RBC count, haemoglobin concentration (Hb), haematocrit and reticulocyte count were the secondary outcome measures.

Power of the study and data analyses

We planned to recruit approximately 60 patients in SWL group and 60 patients in parenchyma-saving surgery group. We wanted to have sufficient power (80%) to detect as statistically significant ($p < 0.05$) the observed post-obstructive differences in any of the outcome measures if the true differences are biologically/clinically significant. We considered that 10% change in any of the outcome measures would be worth observing. In worst case of Epo, the variability of the outcome measure (defined as the coefficient of variation of repeated estimates) was taken to be 20%, as derived from the independent laboratory data. This required about 34 patients in each group. From our previous studies [3, 4] we assessed that up to 30% of recruited patients could be dropped from the analysis, presenting with residual or recurrent stone at 3 months. This increased the sample sizes to about 50 patients in each group. We further increased these numbers to 60 patients in each group to account for gender specificity of secondary outcome measures. Haematological parameters were compared between two groups of patients and controls by analysis of variance. The possible confounding effect of age was tested by including age as a covariate. The post-obstructive changes in outcome variables were statistically evaluated with repeated measures *t* test (two groups compared) or repeated measures analysis of variance (3 groups compared). In case of Epo, due to non-symmetric distribution, the log-transformed data were tested.

Ethics

The patients gave their informed consent and the study was approved by the Ethics Committee of the University Hospital Split.

Results

We recruited 122 patients with unilateral urinary obstruction. All 62 patients treated with SWL had stone in the pyelon and ureteropelvic junction, while out of 60 parenchyma-saving surgery patients 39 were treated with pyelolithotomy, 9 with ureteroscopy and 12 with ureterolithotomy.

Patients' baseline characteristics and therapy outcome

The groups were anthropometrically matched, but differed in the stone size, location and baseline renal function (Table 1). The residual stone fragments (concrements larger than 5 mm immediately after treatment) were seen in six SWL patients and in seven operated patients. They were treated by SWL after the follow-up period. During the follow-up period the recurrent stones (concrements larger than 5 mm at 3 months, but not immediately after treatment) developed in seven SWL patients and in three parenchyma-saving surgery patients. Thus, at 3 months follow-up there were similar stone-free rates in both groups (absence of stone concrements larger than 5 mm).

Baseline haematological variables in persons with and without urinary obstruction

The two groups of control patients were practically identical with regard to haematological parameters, which allowed us to use them as a single control group and proved the absence of the sampling bias (Table 2). Patients scheduled for parenchyma-saving surgery had depressed haematological parameters, and so had the female patients scheduled for SWL, albeit to a minor extent. Epo serum

Table 1 Baseline characteristics and clinical outcome of patients with urinary stones treated with parenchyma-saving surgery or extracorporeal shock waves lithotripsy (SWL)

	Operation ($N = 60$)	SWL ($N = 62$)
Baseline characteristics		
Men/women	26/34	31/31
Age in years (SD)	52 (14)	50 (12)
Height in cm (SD)	169 (15)	172 (9)
Body mass in kg (SD)	80 (19)	80 (14)
Creatinine in μmol/L (SD)	107.2 (32)	90.6 (22)
Stone location (no. in pyelon/no. in ureter)	21/39	62/0
Stone size in cm (SD)	2.6 (1.3)	1.5 (0.7)
Calcium stone (no. patients)	36	38
Infecting stone (no. patients)	31	29
Obstructing stone (no. patients)	54	38
Clinical outcome		
Intrarenal haematoma (no. patients)	0	2
Persistent infection (no. patients)	3	1
Stone-free rate at 3 months (%)	50/60 (83)	49/62 (79)

Table 2 Haematological parameters in two groups of male and female control persons

	Hospital control	Outpatient control
Men (*N*)	75	135
Red blood cell count (10^{12}/L)	5.02 (0.36)	5.08 (0.33)
Haemoglobin (g/L)	149.5 (10)	149.4 (9)
Haematocrit	0.443 (0.03)	0.449 (0.03)
Reticulocyte count (%)	1.80 (0.37)	1.82 (0.76)
Women (*N*)	68	55
Red blood cell count (10^{12}/L)	4.553 (0.3)	4.596 (0.3)
Haemoglobin (g/L)	134.4 (9)	134.1 (10)
Haematocrit	0.411 (0.02)	0.411 (0.03)
Reticulocyte count (%)	1.61 (0.5)	1.53 (0.6)

Values are expressed in means and standard deviations

levels were mildly reduced in SWL patients and halved in parenchyma-saving surgery group (Table 3). The groups were well balanced with respect to age; therefore, the adjustment for age did not produce the material differences in *p* values (data not presented).

The effects of relief of urinary obstruction

At 3 months following relief of obstruction there were 50 patients treated with parenchyma-saving surgery and 49 patients treated with SWL, without residual or recurrent urinary stone. Epo serum levels completely recovered in parenchyma-saving surgery group, but remained unchanged (slightly reduced compared to controls) in SWL group. In parenchyma-saving surgery group the haematological parameters partially recovered, but the improvements were consistent, resulting in relatively precise estimates, whereas in SWL group the effects of treatment were minor and in both directions (Table 4). The results for patients with residual or recurrent stone at 3 months were similar (data not presented).

Open surgery versus ureteroscopy

The surgical group comprised the patients who underwent surgical lithotomy as well as ureteroscopy and these two subgroups differed at presentation, most notably in gender composition and stone size. There was only one woman out of six patients in ureteroscopy group without residual or recurrent stone at 3 months and they presented with much smaller stone then patients in open surgery group, where 59% of patients were women (Table 5). Apparently, at 3 months after surgery the ureteroscopy group recovered more fully in terms of Epo and reticulocyte count, while the baseline value and the changes in parameters of RBC count cannot be compared between the groups due to different gender composition (Table 5). However, due to post hoc nature of these comparisons and small sample size of the ureteroscopy group, these results should be considered only informative, not inferential and no formal statistical comparison was considered appropriate. Anyhow the 6 patients treated with ureteroscopy were unlikely to bias significantly the comparison of 50 operated patients with 49 patients treated by SWL.

Table 3 Haematological parameters and serum erythropoietin concentration (Epo) in male and female patients with urinary stones scheduled for parenchyma-saving surgery or extracorporeal shock wave lithotripsy (SWL) and in control persons

	Operation	SWL	Controls	*P* values		
				Operation versus controls	SWL versus controls	Operation versus SWL
Men (*N*)	26	31	210			
Red blood cell count (10^{12}/L)	4.55 (0.6)	5.03 (0.5)	5.05 (0.4)	<0.0001	0.96	<0.0001
Haemoglobin (g/L)	134 (15)	146 (10)	150 (9.5)	<0.0001	0.11	<0.0001
Haematocrit	0.42 (0.04)	0.44 (0.03)	0.45 (0.03)	<0.0001	0.53	0.002
Reticulocyte count (%)	1.41 (0.9)	1.54 (0.7)	1.82 (0.7)	0.02	0.14	0.73
Age (years)	51.9 (13.6)	49.5 (12.3)	50.6 (17.8)			
Women (*N*)	34	31	123			
Red blood cell count (10^{12}/L)	3.76 (0.3)	4.15 (0.8)	4.57 (0.3)	<0.0001	0.0001	0.004
Haemoglobin (g/L)	115 (14)	129 (13)	134 (9)	<0.0001	0.02	<0.0001
Haematocrit	0.39 (0.04)	0.38 (0.04)	0.41 (0.03)	<0.0001	<0.0001	0.75
Reticulocyte count (%)	1.21 (0.7)	1.19 (0.4)	1.58 (0.5)	0.002	0.002	0.99
Age in years	49.9 (12.2)	49.8 (12.7)	48.8 (13.7)			
Men and women (*N*)	60	62	60			
Erythropoietin (IU/mL)	11.3 (6)	14.7 (7)	18.5 (5)	0.0007	0.048	0.21

Values are expressed in means and standard deviations. *P* values were assessed using post hoc Tukey HSD test, following significant overall results (i.e. $P < 0.05$) of analysis of variance; in case of Epo the variables were first logarithmically transformed

Table 4 Changes in haematological parameters and serum erythropoietin concentration after relief of urinary obstruction by parenchyma-saving surgery that saves the renal parenchyma or extracorporeal shock waves lithotripsy (SWL) in patients without residual or recurrent stone at 3 months

	Baseline	After 3 months	Change (%) (95% CI)	*P* values
Operation ($N = 50$)				
Red blood cell count (10^{12}/L)	4.10 (0.8)	4.35 (0.8)	6.1 (3.9 to 8.4)	<0.0001
Haemoglobin (g/L)	123 (17)	134 (14)	8.9 (6.7 to 10.8)	<0.0001
Haematocrit	0.398 (0.04)	0.429 (0.04)	7.8 (6.2 to 9.0)	<0.0001
Reticulocyte count (%)	1.29 (0.8)	1.56 (1.0)	21 (0 to 40)	0.054
Erythropoietin (IU/mL)	11.5 (6)	18.6 (9)	62 (34 to 91)	<0.0001
SWL ($N = 49$)				
Red blood cell count (10^{12}/L)	4.59 (0.8)	4.46 (0.7)	−2.8 (−5.2 to −0.2)	0.034
Haemoglobin (g/L)	137 (14)	134 (16)	−2.2 (−3.5 to 0.3)	0.055
Haematocrit	0.41 (0.05)	0.43 (0.05)	4.9 (5.4 to 24)	0.024
Reticulocyte count (%)	1.36 (0.6)	1.53 (0.7)	12.5 (6.8 to 19)	<0.0001
Erythropoietin (IU/mL)	15.4 (7)	15.5 (7)	0.7 (−21 to 21)	0.91

Values are expressed as means and standard deviations or 95% confidence intervals (95% CI). *P* values were assessed by paired *t* test; in case of erythropoietin the variables were first logarithmically transformed

Table 5 Baseline characteristics and study outcomes according to type of surgical treatment of urinary stones in patients without residual or recurrent disease at 3 months

	Open surgery ($N = 44$)	Ureteroscopy ($N = 6$)
At presentation		
Men/women	18/26	5/1
Median of age in years (range)	53 (26–82)	51 (23–70)
Stone size in cm (SD)	2.6 (1.2)	0.8 (0.1)
Obstructing stone (no. patients)	38	6
Red blood cell count in 10^{12}/L (SD)	4.2 (0.7)	4.6 (0.3)
Percent change at 3 months		
Red blood cell count	7	2
Haemoglobin	9	2
Haematocrit	8	3
Reticulocyte count	16	29
Erythropoietin	58	80

Discussion

The first new finding of this report is that even partial unilateral human urinary obstruction is related to depressed erythropoietin serum levels. In patients with relatively great obstruction, the erythropoietin serum concentration was largely reduced and haematological parameters differed materially from control values. Thus, the patients with urinary stones were in relative anaemia compared to controls without urinary stones. It appears that urinary obstruction compromises the function of kidney peritubular cells that secrete erythropoietin, and that the unobstructed kidney does not compensate for it. Since kidney or urethral obstruction is a common morbidity these effects should not be underestimated, especially in patients with comorbidity that affects the blood homeostasis.

The vast majority of Epo population is produced in the kidneys, probably by the peritubular cells located mainly in deeper cortical regions [19, 20]. The rate of renal Epo production correlates with tissue hypoxia, although there may be other control mechanisms [19–21]. In our patients, lowered Epo serum concentration was probably caused by depressed secretion of Epo by the obstructed kidney. Two possibilities should be considered: the obstructed kidney Epo-producing cells were receiving the attenuation control signals (tissue hyperoxia) or these cells were not functioning normally. Indeed, in animal models it has been shown that ureteral obstruction causes redistribution of blood flow from medullary to deeper cortical regions [22, 23]. Since Epo-producing cells are mainly located in deeper cortical regions, one may conclude that the blood flow towards Epo-producing cells was increased, leading to tissue hyperoxia and consequent reduction of Epo production. However, this is highly unlikely; urinary obstruction, by an unknown mechanism increases the renal vascular resistance [4], leading to a large reduction of renal blood flow. In a similar cohort of patients with urinary obstruction, we observed the decreases in effective renal plasma flow for 73% (parenchyma-saving surgery group) and 48% (SWL group). It is hardly possible that eventual cortical redistribution of blood flow might overcome these overall reductions in blood flow to result in local tissue hyperoxia. Thus, reduced Epo production should rather be related to abnormal function of obstructed kidney Epo-producing cells.

Besides previously observed effects on renal filtration rate, blood flow and arterial blood pressure [3, 4], this study shows that urinary obstruction also affects the renal control of erythropoiesis. All these effects appeared reversible, as shown on the model of parenchyma-saving surgery. However, at 3 months following surgical relief of obstruction only Epo levels fully recovered, while haematological parameters improved half the way towards the control values. One possibility is that 3 months was not sufficient for the recovered erythropoietin levels to fully restore RBC and related haematological parameters. In SWL patients the relief of obstruction had no chronic effects on Epo and haematological parameters; they were moderately decreased with respect to control values both before and at 3 months after SWL.

This is our third parallel study of SWL and parenchyma-saving surgery on the similar cohort of patients with urinary stones, providing evidences that urinary obstruction causes multiple kidney dysfunctions. All three studies [3, 4, and this report) raise suspicion that SWL causes chronic kidney lesions, which are obscured by beneficial effects of relief of obstruction. These suspicions rest on the observed improvements of kidney functions after parenchyma-saving surgery, but not after SWL. These suspicions cannot be considered as evidences due to lack of control group of patients similar to SWL patients, treated with parenchymal saving procedure. The patients experiencing spontaneous stone passage are less obstructed than SWL patients and cannot be used as controls. The other methods of urinary stone removal like percutaneous nephrolithotripsy cannot guarantee the absence of either direct mechanical renal injury, or injury mediated by imperfect focusing of ultrasound waves. The best control group would be achieved by randomizing similar patients to SWL or parenchyma-saving surgery, which, however, would currently be considered non-ethical. Bearing these limitations in mind, the absence of chronic improvements in kidney function in SWL patients suggests the presence of serious, unrecognized chronic adverse effects of this method, which should be weighted against its simplicity and noninvasiveness.

In conclusion, obstructive uropathy is associated with depressed erythropoietin serum concentration and reduced red blood cell count. The reversible nature of these impairments was seen at 3 months following the parenchyma-saving surgery, but not the extracorporeal lithotripsy.

Acknowledgments This research was partially funded by the grant 216-0000-0216 the Croatian Ministry of Science, Technology and Sports.

References

1. Bomanji J, Boddy SA, Britton KE, Nimmon CC, Whitfield HN (1987) Radionuclide evaluation pre- and postextracorporeal shock wave lithotripsy for renal calculi. J Nucl Med 28:1284–1289
2. Gupta M, Bolton DM, Irby P III, Hubner W, Wolf JS Jr, Hattner RS, Stoller ML (1995) The effect of newer generation lithotripsy upon renal function assessed by nuclear scintigraphy. J Urol 154:947–950
3. Eterovic D, Juretic-Kuscic Lj, Capkun V, Dujic Z (1999) Pyelolithotomy improves while extracorporeal lithotripsy impairs kidney function. J Urol 161:39–44
4. Eterovic D, Situm M, Juretic-Kuscic Lj, Dujic Z (2005) A decrease in blood pressure following pyelolithotomy but not extracorporeal lithotripsy. Urol Res 33:93–98
5. Jelkmann W (2004) Molecular biology of erythropoietin. Intern Med 43:649–659
6. Santoro A (2002) Anemia in renal insufficiency. Rev Clin Exp Hematol 1:12–20
7. Eschbach JW (1989) The anemia of chronic renal failure: pathophysiology and the effects of recombinant erythropoietin. Kidney Int 35:134–148
8. Chandra M, Clemons GK, McVicar MI (1988) Relation of serum erythropoietin levels to renal excretory function: evidence for lowered set point for erythropoietin production in chronic renal failure. J Pediatr 113:1015–1021
9. McGonigle RJ, Wallin JD, Shadduck RK, Fisher JW (1984) Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency. Kidney Int 25:437–444
10. Radtke HW, Claussner A, Erbes PM, Scheuermann EH, Schoeppe W, Koch KM (1979) Serum erythropoietin concentration in chronic renal failure: relationship to degree of anemia and excretory renal function. Blood 54:877–884
11. Jelkmann W, Marienhoff N, Giesselmann S, Busch L (1988) Lowered plasma erythropoietin in hypoxic rats with kidney tubule lesions. Blut 57:317–321
12. Maxwell PH, Ferguson DJ, Nicholls LG, Johnson MH, Ratcliffe PJ (1997) The interstitial response to renal injury: fibroblast-like cells show phenotypic changes and have reduced potential for erythropoietin gene expression. Kidney Int 52:715–724
13. Maxwell PH, Ferguson DJ, Nicholls LG, Iredale JP, Pugh CW, Johnson MH, Ratcliffe PJ (1997) Sites of erythropoietin production. Kidney Int 51:393–401
14. Tan CC, Eckardt KU, Ratcliffe PJ (1991) Organ distribution of erythropoietin messenger RNA in normal and uremic rats. Kidney Int 40:69–76
15. Tan CC, Tan LH, Eckardt KU (1996) Erythropoietin production in rats with post-ischemic acute renal failure. Kidney Int 50:1958–1964
16. Priyadarshi A, Periyasamy S, Burka TJ, Britton SL, Malhotra D, Shapiro JI (2002) Effects of reduction of renal mass on renal oxygen tension and erythropoietin production in the rat. Kidney Int 61:542–546
17. Necas E, Ponka P (1998) Ureter obliteration transiently depresses erythropoietin production. Eur J Clin Invest 28:918–923
18. Tsukada Y, Murata N, Yano S, Naruse T (1994) Transient suppression of erythropoietin synthesis in hydronephrosis. Nephron 68:282–283
19. Fisher JW (2003) Erythropoietin: physiology and pharmacology update. Exp Biol Med 28:1–14
20. Kendall RG (2001) Erythropoietin. Clin Lab Haematol 23:71–80
21. Eckardt KU, Kurtz A, Bauer C (1989) Regulation of erythropoietin production is related to proximal tubular function. Am J Physiol 256:F942–F947
22. Campbell MF, Walsh CW, Retik AB (eds) (2002) Campbell's urology, 8th edn. Saunders Company, Philadelphia, pp 342–385
23. Freudenthaler SM, Lucht I, Schenk T, Brink M, Gleiter CH (2000) Dose-dependent effect of angiotensin II on human erythropoietin production. Pflugers Arch 439:838–844