

Role of Contrast-Enhanced Voiding Urosonography in the Evaluation of Renal Transplant Reflux – Comparison with Voiding Cystourethrography and a New Classification

Rolle der Kontrastmittelverstärkten Miktionsurosonografie bei der Bewertung des Reflux in Nierentransplantate – Vergleich mit der Miktionszystourethrografie und einer neuen Klassifikation

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ABSTRACT

Vesicoureteral reflux (VUR) is a common urological complication in renal transplant patients. **The aim** of this study is to evaluate the performance of contrast-enhanced voiding urosonography (CEvUS) in the diagnosis and classification of reflux into the renal allograft, to evaluate and classify VUR into the allograft using voiding cystourethrography (VCUG) and CEvUS, to compare the two methods, and to propose a new classification of reflux into the allograft based on CEvUS and VCUG assessment, in line with the international reflux grading system.

Materials and Methods From January 2017 to July 2019, 84 kidney transplant patients were enrolled. All patients underwent VCUG and CEvUS.

Results In 76 cases there was agreement between VCUG and CEvUS (90 %) (Kappa = 0.7). The sensitivity of CEvUS using VCUG as the gold standard was 90 %, and the specificity was 92 %. Of the 7 cases diagnosed by VCUG and not by CEvUS, 6 were grade 1 and 1 was grade 2.

Conclusion Transplant patients with reflux symptoms should undergo CEvUS. If the outcome is negative, VCUG should be performed. The classification that we propose is better suited to describe VUR in transplant patients, because it is simpler and takes into account whether reflux occurs not only during urination but also when the bladder is relaxed.

ZUSAMMENFASSUNG

Vesikoureteraler Reflux (VUR) ist eine häufige urologische Komplikation bei Patienten mit Nierentransplantation.

Ziel dieser Studie ist es, die Leistung der Kontrastmittelverstärkten Miktionsurosonografie (CEmUS) bei der Diagnose und Klassifizierung des Reflux in das Nieren-Allotransplantat zu bewerten, den VUR in das Allotransplantat mittels Miktionszystourethrografie (MCU) und CEmUS zu bewerten und zu klassifizieren, die beiden Methoden zu vergleichen und eine neue Klassifikation des Reflux in das Allotransplantat basierend auf der CEmUS- und MCU-Beurteilung in Übereinstimmung mit dem internationalen Reflux-Klassifikationssystem vorzuschlagen.

Material und Methoden Von Januar 2017 bis Juli 2019 wurden 84 nierentransplantierte Patienten eingeschlossen. Bei allen Patienten wurden MCU und CEmUS durchgeführt.

Ergebnisse In 76 Fällen bestand Übereinstimmung zwischen MCU und CEmUS (90 %) (Kappa = 0,7). Die Sensitivität von CEmUS bei Verwendung der MCU als Goldstandard betrug 90 %, die Spezifität betrug 92 %. Von den 7 Fällen, die mittels MCU, aber nicht durch CEmUS diagnostiziert wurden, hatten 6 Patienten Grad 1 und 1 Patient hatte Grad 2.

Schlussfolgerung Transplantationspatienten mit Refluxsymptomen sollten sich einer CEmUS unterziehen. Wenn das Ergebnis negativ ist, sollte eine MCU durchgeführt werden. Die von uns vorgeschlagene Klassifikation ist besser geeignet, um den VUR bei Transplantationspatienten zu beschreiben, da sie einfacher ist und berücksichtigt, ob der Reflux nicht nur bei der Blasenentleerung, sondern auch bei entspannter Blase auftritt.

Introduction

Vesicoureteral reflux (VUR) is a retrograde flow of urine from the urinary bladder to the ureter and collection duct system. In non-transplant patients, this condition is caused by an abnormal congenital development of the ureterovesical junction or an increase in bladder pressure due to bladder neck obstruction or dysfunctional urination. In kidney transplant patients, VUR is a common urological complication with an incidence that varies widely in the literature [1–4].

In kidney transplantation, ureteroneocystostomy has gradually shifted from more invasive to less invasive techniques. The initial technique, ascribed to Politano-Ledbetter, included an extended cystotomy, creation of a submucosal tunnel, and anastomosis of the ureter to the bladder from the inside of the bladder. The incidence of reflux associated with this procedure was low but stenosis was frequent [5]. The Lich-Gregoir extravascular tunneling technique is most commonly used today. It includes exposure of about 3 cm of the mucous layer after incision of the muscular layer, anastomosis of the ureter to the mucosa, and partial closure of the muscular layer in order to create a submucosal tunnel. This technique increases the incidence of reflux, but stenosis is less frequent [2, 6, 7].

VUR is most frequent in patients with a low residual urinary output and a defunctionalized bladder, as it is difficult to create a submucosal tunnel long enough for adequate implantation in this type of bladder, and the result is high intravesical pressure after re-functionalization [8]. Another risk factor for VUR is high bladder pressure due to reduced bladder capacity [1].

VUR damages the urinary tract by causing bacterial infections and increased hydrostatic pressure, although recent studies have not supported the hypothesis that VUR is an important cause of late renal graft failure [4].

Bacteria from the lower urinary tract can easily contaminate the upper tract also because the ureter is very short, thus resulting in recurrent parenchymal infections and possibly further complications. Acute pyelonephritis (PNA) is a major infectious complication in graft recipients with a cumulative incidence of 19–23 % reported in the literature [9].

The aim of the study is to:

- evaluate the capability of contrast-enhanced voiding urosonography (CEVUS) in the diagnosis and classification of VUR into the renal allograft;

- evaluate and classify VUR into the renal allograft using voiding cystourethrography (VCUG) comparing CEVUS and VCUG;
- propose a new classification of VUR into the renal allograft based on CEVUS and VCUG, in line with the international grading system that we consider too complex for transplant patients. In fact, the reason for VUR is almost exclusively linked to the surgical technique. We believe that simplification makes it easier to identify the problem and establish the subsequent therapy.

Materials and methods

Patient population

From January 2017 to July 2019, 84 patients were enrolled 8–16 months after kidney transplantation (26 females and 59 males; mean age 63 (range: 42–78)). The mean duration of pretransplant hemodialysis was 7 years.

Inclusion criteria were:

- duration of pretransplant hemodialysis from 1 to 10 years.
- acute inflammatory symptoms (fever, leukocytosis, high levels of C-reactive protein);
- at least two past febrile urinary tract infections (UTIs)
- signs of renal dysfunction (increase in creatinine level);
- ureteral implantation carried out using Lich's extravascular technique without stenting;
- the patient had received antibiotic prophylaxis

Exclusion criteria were:

- other acute pathologies (acute rejection, acute tubular necrosis, etc.), excluded by biopsy
- kidney transplantation combined with other organs (pancreas, liver)
- previous kidney transplantation

Imaging acquisition and interpretation

All patients underwent:

- retrograde cystourethrography performed with X-ray (Siregraph CF, Siemens); images were saved in the course of fluoroscopy. During filling, multiple spot images in the anteroposterior, oblique, and lateral positions were obtained as well as urethral images during voiding. Contrast agent: 100 ml (Iopamiro 370 mg/ml; Bracco, Milan) was administered using a transurethral bladder catheter and

followed by up to 150 ml sterile saline solution. The mean duration of VCUG examination was 20 minutes (range: 15–25 minutes).

Radiograms were evaluated by two expert radiologists following a double-blind procedure.

- All CEvUS examinations were performed by one radiologist with many years of ultrasonography (US) expertise, who was blinded to the VCUG results. The US equipment was Samsung RS80A with Prestige using a 3.5–5 MHz curvilinear probe. US was performed after adequate hydration of the patient. Contrast agent (0.5 ml SonoVue, Bracco, Milan, diluted in 250 ml 0.9% saline) was slowly instilled using a transurethral bladder catheter under US control [10]. The mean duration of CEvUS examination was 15 minutes (range: 10–20 minutes). CEvUS images were saved both as single multiple images and as video clips.

- microbiological and urine culture examination was carried out to identify and characterize a possible urinary tract infection (UTI).

We performed VCUG and CEvUS after antibiotic therapy (8–10 days since the last UTI). Each patient underwent VCUG, and then CEvUS after 3–10 days.

Methods

Cystourethrography involves two stages: retrograde urethrography and urinary cystourethrography. The bladder is filled with contrast agent using a Foley catheter, and the patient then undergoes intermittent fluoroscopy while the bladder is being dilated by the contrast agent.

In this phase we can evaluate bladder shape and contours, filling defects or other anomalies, onset of reflux during filling, and degree of reflux. In the second stage, the patient initiates voiding. X-rays are taken to evaluate the urethra during urination and the presence of VUR.

CEvUS includes B-mode US evaluation of the kidneys and bladder to assess renal size, maximum bladder volume (formula: volume = length × width × height × 0.52), wall thickness, antero-posterior diameter of the renal pelvis, and presence of focal and non-focal pathologies, and finally color Doppler examination provides renal flow indices (resistive index, pulsatility index). The second step involves the use of intravesical contrast agent diluted in normal sterile saline and repeated imaging of the bladder and kidneys using CEvUS during and after bladder filling and while voiding.

The International Classification of Vesicoureteral Reflux (► **Table 1**) is the grading system currently used for VUR. In this study we propose a new and different classification system for VUR in transplant patients using CEvUS (► **Table 2**).

Ethical approval for this study was granted by the Medical Research Ethics Committee of our institution, and informed consent was obtained from all patients. According to the current privacy law, all patients were guaranteed privacy protection and proper use of personal data.

Statistical Analysis

Continuous variables were reported as means and ranges. Categorical variables were reported as numbers and percentages. No

► **Table 1** International Classification of Vesicoureteral Reflux.

| | |
|------------------|---|
| grade I | ureter only |
| grade II | ureter, pelvis, and calyces; no dilatation, normal calyceal fornices |
| grade III | Mild or moderate dilatation and/or tortuosity of the ureter and mild or moderate dilatation of the renal pelvis. No or slight blunting of the fornices |
| grade IV | Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calyces. Complete obliteration of the sharp angle of the fornices but maintenance of the papillary impressions in the majority of calyces |
| grade V | Gross dilatation and tortuosity of the ureter. Gross dilatation of the renal pelvis and calyces. The papillary impressions are no longer visible in the majority of the calyces. |

► **Table 2** Proposed classification of reflux grading based on VCUG and CEvUS in transplanted kidneys.

| | |
|----------------|--|
| grade 0 | no reflux |
| grade 1 | during voiding, urine flows back up the ureter only and the renal pelvis is not visualized at cystography and CEvUS |
| grade 2 | during voiding urine flows back into the ureter, renal pelvis, and calyces A) no damage B) damage (pelvis and ureter appear dilatated with or without presence of clubbing of the calyces and scars) |
| Grade 3 | reflux without voiding strain |

missing data were reported in the investigated variables. Fisher's exact test was used for comparisons of categorical variables.

Agreement between VCUG and CEvUS was calculated using the Cohen's Kappa method. A kappa coefficient value <0 indicates no agreement, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect agreement. Linear regression was used to analyze the correlation between the duration of preoperative dialysis and bladder capacity. Pearson's r coefficient was estimated with this intent. A value of 1 indicates perfect linear correlation between the two variables.

Variables with a p-value <0.05 were considered statistically significant. We used the SPSS statistical package version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

No clinically significant contrast agent-related side effects were experienced by the patients. Both examinations and different contrast agents were well tolerated.

The inter-observer variability in the evaluation of VCUG was less than 3% of cases.

► **Table 3** Contrast-enhanced voiding urosonography (CEvUS) and voiding cystourethrography (VCUG) in the detection of vesico-ureteral reflux (VUR).

| | VUR | No VUR |
|--------------|-----|--------|
| CEvUS | 66 | 18 |
| VCUG | 72 | 12 |
| agreement | 65 | 11 |
| disagreement | 7 | 1 |

► **Table 4** Sensitivity, specificity, and Kappa value CEvUS.

| | |
|---|------|
| sensitivity | 90 % |
| specificity | 92 % |
| observed proportionate agreement (po) | 0.9 |
| expected probability that both CEvUS and VCUG diagnosed VUR at random | 0.02 |
| overall random agreement probability (Pe) | 0.7 |
| Kappa value | 0.7 |

Among the 84 patients enrolled:

- VCUG detected VUR in 72 patients (86%); no reflux was observed in 12 (14%).
- CEvUS detected VUR in 66 patients (79%); no reflux was observed in 18 patients (21%).

VCUG detected VUR in 72 patients; in 65 of these CEvUS also detected VUR.

VCUG outcome was negative in 12 patients; in 11 of these CEvUS was also negative.

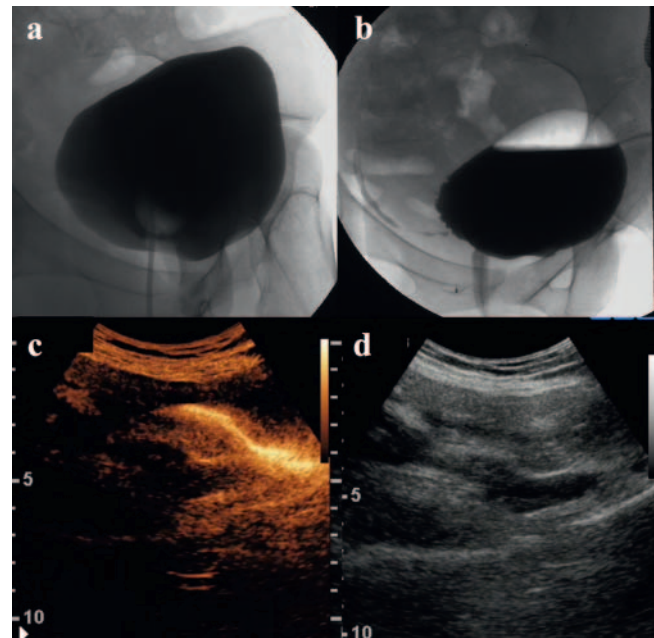
In 76 cases there was agreement between the two methods (90%), whereas in 8 cases (10%) there was no agreement (► **Table 3**). The Kappa method showed overall agreement = 0.7 between VCUG and CEvUS. Using VCUG as the gold standard, the sensitivity of CEvUS was 90% and the specificity was 92% (► **Table 4**).

In patients with reflux, the degree of reflux was also assessed using both methods. This is the outcome using our “new” classification system:

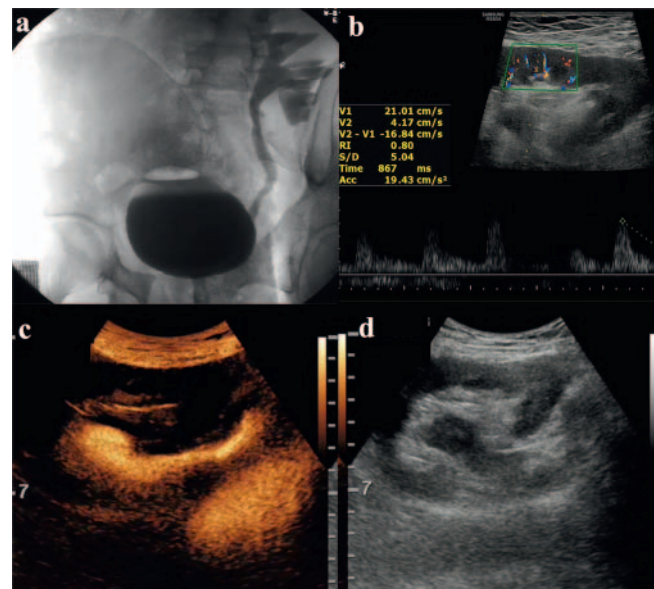
Out of 66 cases of VUR detected by CEvUS, 17 were classified as grade 1 (26%) (► **Fig. 1**), 41 as grade 2 (62%) (► **Fig. 2**), and 8 as grade 3 (12%) (► **Fig. 3**). Out of the 41 patients classified as grade 2, 33 were categorized as grade 2A and 8 as grade 2B.

Out of 72 cases of VUR detected by VCUG, 18 were classified as grade 1 (25%), 47 as grade 2 (65%), and 7 as grade 3 (10%). Out of the 47 patients classified as grade 2, 38 were categorized as grade 2A and 9 as grade 2B.

Distribution of positivity using the two methods was evaluated according to the degree of reflux. Out of the 7 cases diagnosed at VCUG but not at CEvUS, 6 were grade 1 and 1 was grade 2, while the one case of VUR diagnosed at CEvUS but not at VCUG was



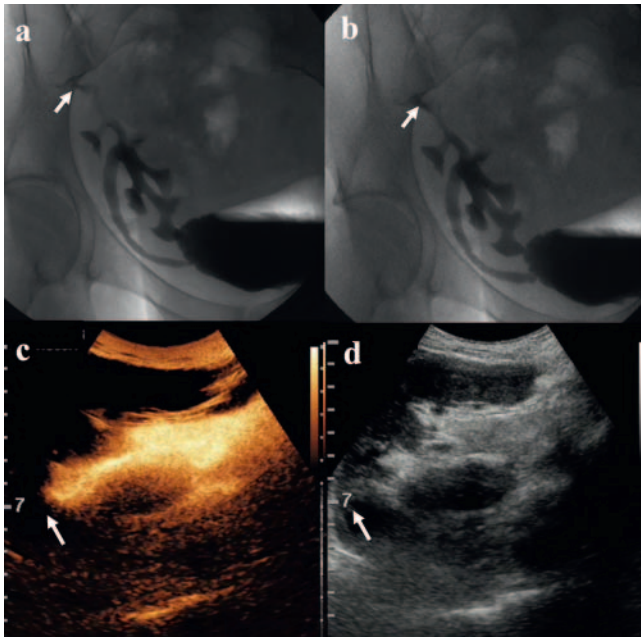
► **Fig. 1** VUR grade 1 according to our classification. **1a** VCUG shows the bladder filled with contrast agent; there is no evidence of reflux at rest; **2a** VCUG shows retrograde passage of contrast agent into the ureter during voiding strain; **1c–d** CEvUS confirms the passage of contrast agent into the ureter during voiding strain.



► **Fig. 2** VUR grade 2B according to our classification. **a** VCUG shows retrograde passage of contrast agent into the ureter, pelvis, and calyces during voiding strain; **b** Color Doppler US examination shows increased resistive index (RI = 0.80); **c, d** CEvUS confirms the passage of contrast agent into the ureter and pelvis during voiding strain.

grade 1. The differences in the degree of reflux in the concordant cases are reported in ► **Fig. 4**.

We performed VCUG and CEvUS in patients with at least two prior febrile UTIs. Among the 71 symptomatic patients with mi-



► **Fig. 3** VUR grade 3 according to our classification. **a, b** VCUG shows retrograde passage of contrast agent into the ureter, pelvis and calyces during the filling phase; note the clubbed calyces in the upper pole (white arrow); **c, d** CEvUS confirms the passage of contrast agent into the ureter and pelvis at rest and shows clubbed calyces and scar in the upper pole (white arrow).

► **Table 5** Duration of pretransplant dialysis, bladder capacity, VUR rate (diagnosed with VCUG).

| duration of dialysis (years) | patients | mean bladder capacity (ml) | VUR rate |
|------------------------------|----------|----------------------------|--------------------|
| <5 | 32 | 300 ml (250–500 ml) | 70 % (23 patients) |
| 5–10 | 52 | 150 ml (30–500 ml) | 90 % (49 patients) |

Some studies in the literature have highlighted the superiority of CEvUS compared to VCUG in the diagnosis of VUR [11, 12]. However, in our study, we found a substantial overlap in results between the two methods, which diagnosed nearly the same number of cases of VUR, CEvUS yielding a sensitivity of 90 % and specificity of 92 %. The agreement between the two methods was quite high (90 %) and the Kappa value was high (0.7).

VCUG showed more cases of VUR compared to CEvUS. However, of the 7 cases that tested positive at VCUG and not at CEvUS, 6 were grade 1 at VCUG. This could be explained by the difficulty of CEvUS in the assessment of low-grade VUR. In addition, the sensitivity of CEvUS may be reduced particularly in low-grade VUR due to posterior attenuation as a result of reflection of the US beam caused by the contrast agent present in the bladder.

The high agreement between the two methods in renal allografts is probably also due to the position of the organ immediately under the muscular fascia and muscular layer in the iliac fossa, as this significantly increases the resolution of the image obtained using different US frequencies (3.5 to 7.5 MHz). On the other hand, VCUG allows a better evaluation of the excretory tract and reveals more anatomic details. VCUG is therefore the preferred method for the detection of VUR [13].

However, a radiation-free method for monitoring VUR would obviously be preferable. VCUG does not provide any information on the renal parenchyma. CEvUS provides assessment of the excretory pathways and also a study of the renal parenchyma showing the presence of possible pathologies, such as pyelonephritis, post-surgical collections, and alterations in vascularization in addition to an abnormal increase in the resistive index on color Doppler. All of this information can be obtained in the course of one examination. Moreover, VCUG gives only a clip of the urinary tract dynamics lasting for several seconds to a couple of minutes, whereas a meticulous CEvUS examination provides more detailed information on the filling and voiding procedure [14]. US contrast agents are also safer than iodate contrast agents, as they carry only a minimal risk and can be safely administered to patients. The incidence of anaphylactoid reactions to US contrast agents is significantly lower than the incidence linked to iodinated contrast agents [15].

Nevertheless, US is an operator-dependent examination, and the quality of the outcome also depends on other factors such as obesity, meteorism, and/or poor patient compliance.

UTI is the most frequent infectious complication reported in the literature, among patients with renal transplant, and it is con-

crobiological and urine culture examinations positive for UTI, 66 patients (92 %) presented VUR diagnosed with both CEvUS and VCUG.

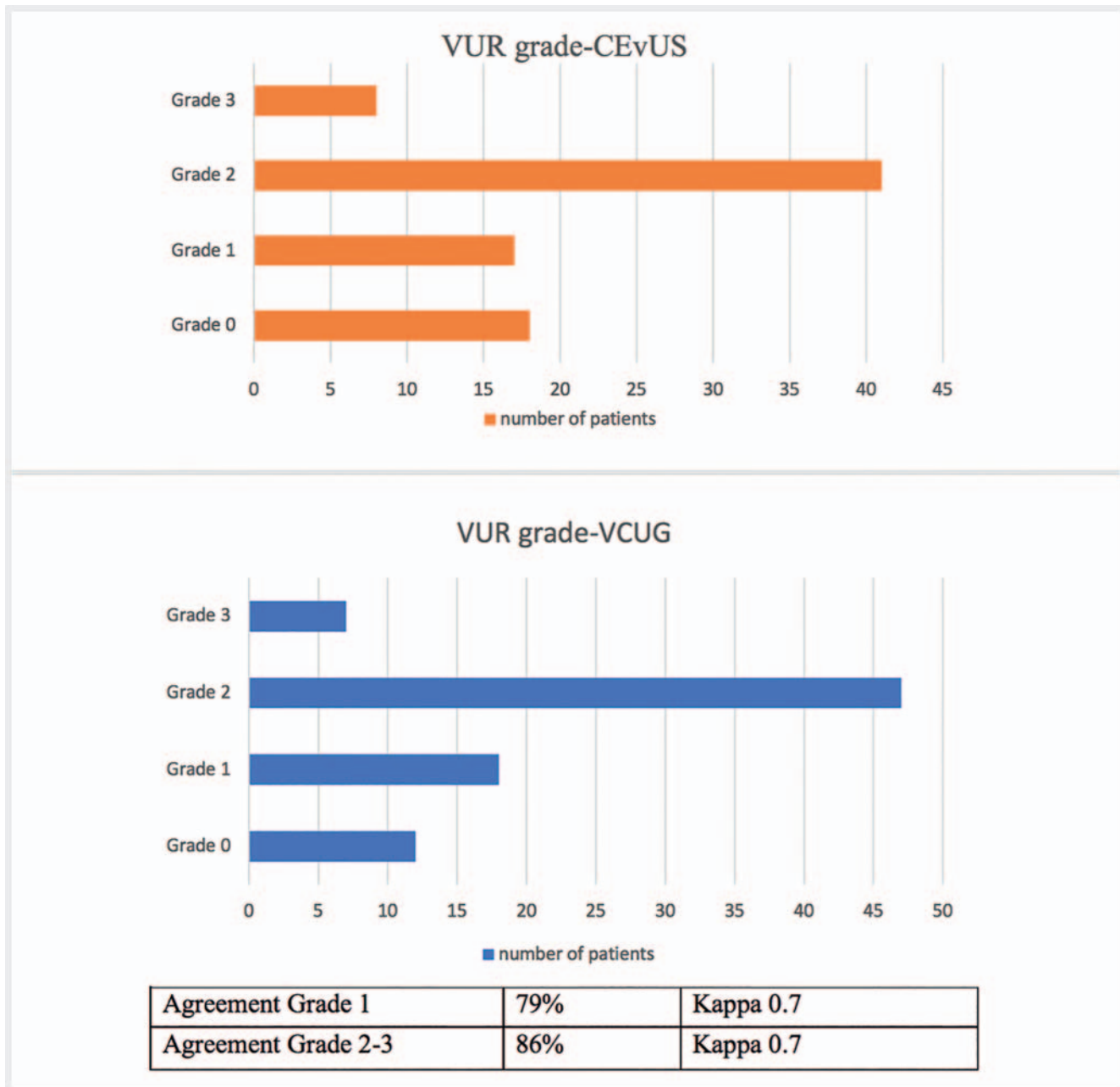
Out of 66 cases of detected VUR, 18 were classified as grade 1, 43 as grade 2 (62 %) and 5 as grade 3. Out of the 43 patients classified as grade 2, 32 were categorized as grade 2A and 11 as grade 2B.

In 16 patients (22 %) VUR was caused by *Klesbiella*, in 33 (47 %) by *Escherichia coli*, in 2 (3 %) by *Enterococcus*, in 14 (20 %) by BKvirus (BKV) and in 6 (8 %) by *Candida Albicans*. CEvUS detected acute pyelonephritis (PNA) in 5 patients with grades 2 and 3 VUR.

Finally, the 84 patients were divided into two groups based on the duration of pre-transplant hemodialysis: group A had undergone hemodialysis for <5 years, group B for 5–10 years. In each group, bladder capacity was calculated using B-mode US (before the administration of contrast agent), revealing a significant difference between the two groups ($p < 0.001$): in group A the mean bladder capacity was 300 ml (range 250–500 ml), in group B it was 150 ml (range 30–500 ml). VUR diagnosed with VCUG was detected more frequently in group B (90 % of cases) than in group A (70 %) (► **Table 5**).

Discussion

In view of our selection criteria, we expected a high prevalence of VUR in this study, and VCUG thus detected VUR in 72 patients (86 %) and CEvUS in 66 patients (79 %).



► **Fig. 4** Sample distribution according to the VUR grade, CEvUS vs. VCUg, and difference in the agreement between the two methods based on the degree of reflux.

sidered the most important risk factor for weak graft function, morbidity, and mortality [16]. The pathogens most frequently encountered in this study were Klebsiella, Escherichia coli, and BKV. Several predisposing factors may promote UTI after kidney transplantation: female gender, age, history of recurrent UTI, diabetes mellitus, urinary tract anomalies, Foley catheter, ureteric catheter, and immunosuppression therapy [17, 18]. Induction therapy with cell depleting antibodies such as anti-thymocyte globulin has been reported to have a higher incidence of UTI. Azathioprine and mycophenolate mofetil lead to bone marrow suppression and neutropenia [17, 18].

Other drugs (calcineurin inhibitors, everolimus) seem not to affect the risk. Steroid withdrawal did not have any effect on the risk of UTI [18].

In this study, bladder capacity was evaluated because there was a correlation between bladder size and degree of reflux. The difference in bladder capacity between group A and group B (divided into groups according to the duration of hemodialysis) is explained by the fact that bladder capacity is significantly reduced after prolonged duration of hemodialysis [19].

The amount of urinary output or its absence could be considered a co-factor responsible for VUR. The incidence of VUR was higher in patients with atrophic bladders, a fact which could be

explained by the difficulty in creating an adequately long submucosal tunnel to prevent VUR.

The international VUR classification is based on the extent of filling and dilatation of the ureter, the renal pelvis, and the calyces especially in children [20].

In transplant patients, VUR is almost exclusively linked to the surgical technique. Moreover, the excretory pathways are shorter in transplanted kidneys than in native kidneys. The International Classification of Vesicoureteral Reflux is suitable for grading reflux in a native kidney, as it perfectly describes the condition of the excretory pathways. However, in a transplant patient the reason for VUR is less complicated. Therefore, we propose a simpler classification, which more clearly describes the reflux affecting a renal allograft. We believe that our classification system is suitable for both VUCG and CEvUS.

With regard to the international classification, some authors have pointed out disagreement in the interpretation of the degree of reflux, especially in the intermediate grades. Kronemer et al. [21] reported that different grade interpretations occurred in 20 of 39 patients with VUR when the same images were read by two radiologists. Metcalfe et al. [22] also analyzed reflux grades and concluded that although the overall VUR grading of VUCG was shown to be reliable, agreement was highest at the extremes of the scale (grades I and V). Scoring discrepancies were more common in the intermediate grades (II–IV).

Our classification includes three grades. Grades 1 and 2 describe urinary reflux during voiding as follows: Grade 1: urine flows back into the ureter, grade 2: urine flows back up the ureter, renal pelvis, and calyces without dilation (subgrade A) or with dilation (subgrade B). In addition, the classification that we propose takes into account whether reflux occurs not only during urination but also when the bladder is relaxed during the filling phase (grade 3 of our classification), a characteristic which is not described in the international VUR grading system [20]. We excluded grades 2A and 2B from our grade 3 because all patients present more or less evident dilatation.

This study has some limitations:

- the patient population was not randomized, as only patients with a high probability of having VUR were included;
- we carried out the examinations 8–16 months after kidney transplantation, so long-term information is lacking. However, most cases of VUR are linked to the surgical technique and it therefore occurs immediately after kidney transplantation;
- we do not have information about urinary output of patients before kidney transplantation. Urinary output could be considered a co-factor causing VUR in transplanted patients who underwent hemodialysis.

In conclusion, CEvUS is a radiation-free examination which presents several advantages compared to VUCG in the diagnosis of vesicoureteral reflux (VUR). Our preliminary results are promising, and we suggest that CEvUS be carried out as a first-line examination in transplant patients presenting with suspected reflux. If CEvUS outcome is negative, VUCG should be performed. For a more correct diagnosis and grading, we propose a new classification which is better suited to describe VUR in kidney transplant patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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