13 Vesicoureteral Reflux and Radionuclide Cystography

S. Ted Treves and Frederick D. Grant

Vesicoureteric reflux (VUR) is the retrograde transit of urine from the urinary bladder to the ureters and kidneys. VUR is caused by a failure of the ureterovesical valve mechanism. This failure may be due to a congenital variation, immaturity, or a pathologic process, such as an infection that distorts the anatomy or function (or both) of the ureterovesical junction. The clinical importance of VUR is its association with pyelonephritis and its contribution to reflux-related nephropathy. Although an evolving field, identification of VUR remains an important part of the evaluation of patients with febrile urinary tract infections, especially those with documented involvement of the kidney as a site of infection [1–5]. VUR also can contribute to nephropathy resulting from the reflux of urine into the renal collecting system without a concurrent infection. Radionuclide cystography (RNC) is a sensitive and easy method for the diagnosis and follow-up of VUR. In conjunction with ^{99m}Tc-DMSA, ultrasonography, and voiding cystourethrography, RNC can be an important part of the evaluation of recurrent febrile urinary tract infections in children.

The Ureterovesical Junction

Passive and active factors characterize the normal valve mechanism of the ureterovesical junction. Passive factors include the obliquity of entry of the ureter into the bladder; the length of the intramural ureter, particularly of its submucosal segment; and the ratio of the length of the submucosal tunnel to the diameter of the ureter. The active factors include the contraction of the ureterotrigonal muscles, which close the ureteral meatus and the submucosal tunnel, and active ureteral peristalsis, as seen during diuresis [6]. The intramural ureter becomes longer with age, often producing sufficient length to convert a refluxing ureterovesical junction into a nonrefluxing one. The principal long-term consequence of VUR, particularly when associated with infection, is the development of pyelonephritis, which in turn

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may lead to scarring, hypertension, and chronic renal failure.

Incidence

The incidence of VUR in the general population is not well-defined. Approximately 1 % (7 of 535) of apparently normal neonates, infants, and children have been found to have VUR [6]. The incidence of VUR in siblings of children with reflux is much greater than in the general population and may be as high as 45 % [7–11]. In a study at Boston Children's Hospital six of 16 refluxing-symptom-free siblings of children with VUR had evidence of cortical renal damage as assessed by technetium-99m-dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy [12–15]. ^{99m}Tc-DMSA cortical scintigraphy provides an early indicator of renal damage, and it can be considered in the assessment of symptomatic and asymptomatic siblings of refluxing children. Using radionuclide cystography, we also have found previously undiagnosed asymptomatic reflux in parents of index children with VUR.

Diagnosis

The imaging method most frequently used for the detection of VUR has been radiographic voiding cystourethrography (VCUG). It provides fine anatomic detail of the bladder and the urethra. In patients with reflux, it clearly outlines the anatomy of the pelvicaliceal systems, the ureters, and their insertion into the bladder. It has some limitations, however, including gonadal radiation exposure and low temporal resolution, which prevents diagnosis of intermittent VUR. In the past decades, radionuclide cystography (RNC) gained increasing acceptance for both the initial diagnosis and follow-up of VUR (Fig. 13.1). Advantages

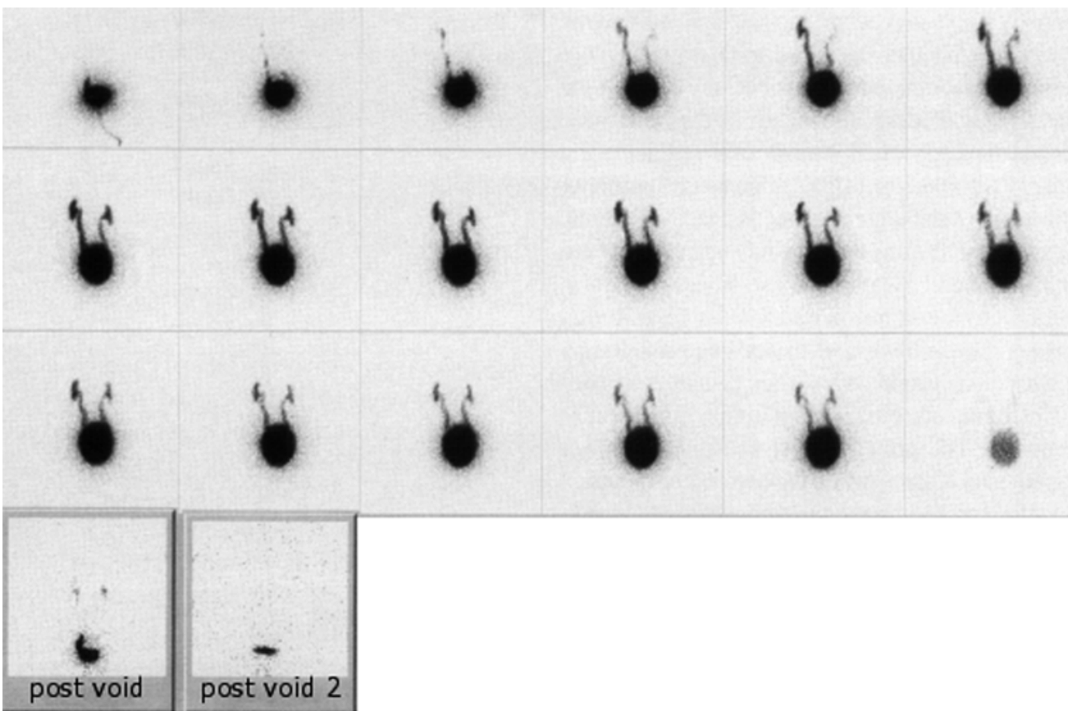


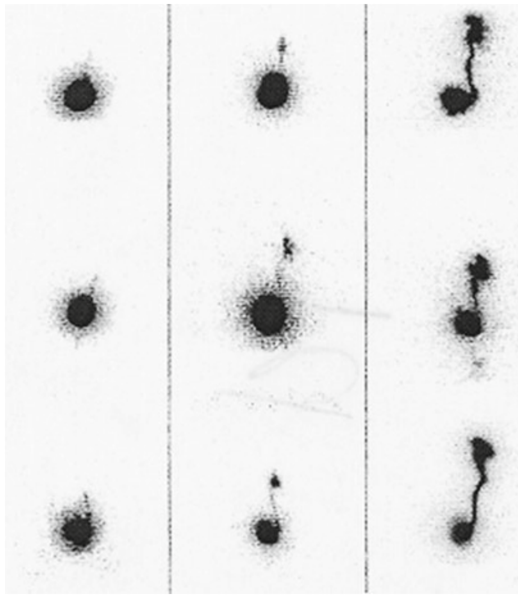
Fig. 13.1 Bilateral vesicoureteric reflux, as shown by radionuclide cystography. Initial left reflux followed by right reflux reaching the renal pelves. Reflux appears early and persists during the entire voiding phase. The patient could not void while on the examination table. Postvoid images reveal complete drainage of tracer from the ureteropelvicaliceal systems

of RNC include lower gonadal radiation exposure, high temporal resolution, and higher sensitivity for the detection of mild VUR. Also RNC may be less expensive to perform than VCUG [16]. However, RNC cannot delineate the anatomy of the bladder and urethra. Therefore, one approach is to to use VCUG for the initial diagnosis of VUR, and then to follow patients with RNC. RNC may be appropriate for the initial diagnosis of VUR in sibling studies and in older girls, in whom excluding urethral valves is not important [17–19].

Grading the Severity of Vesicoureteric Reflux

The severity of VUR has been classified by its morphologic appearance on VCUG or RNC. A report by an international group studying VUR adopted a VCUG classification of reflux illustrated in Fig. 13.2 [20]. This grading system is convenient for communication but need not be applied rigidly in an individual case [6]. Moreover, this classification is not exact, as VUR appearances vary over a continuum and often some VURs do not fall precisely within one of the five grades. For example, the same patient may be classified with a grade II reflux during one examination and a grade I or III at another.

With RNC it is possible to recognize at least three degrees of reflux severity (Fig. 13.3) [21]. The least severe degree shows reflux limited to the



RNC Grade 1 RNC Grade 2 RNC Grade 3

Fig. 13.3 Reflux severity in radionuclide cystography (RNC)

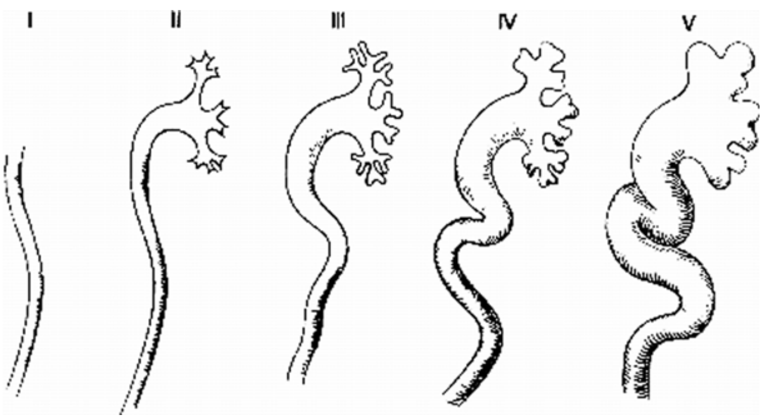


Fig. 13.2 Grading of vesicoureteral reflux by voiding cystourethrography, international study classification. Grade *I*: ureter only. Grade *II*: ureter, pelvis, and calyces; no dilatation, normal caliceal fornices. Grade *III*: mild or moderate dilatation or tortuosity of ureter (or both) and mild or moderate dilatation of renal pelvis but no or slight blunting of fornices. Grade *IV*: moderate dilatation or tortuosity of ureter (or both) and moderate dilatation of renal pelvis and calyces. Complete obliteration of sharp angles of fornices but maintenance of papillary impressions in majority of calyces. Grade *V*: gross dilatation and tortuosity of ureter; gross dilatation of renal pelvis and calyces; papillary impressions are no longer visible in most calyces

distal ureter without reaching the renal pelvis (Fig. 13.4). This corresponds to grade I reflux and can be called RNC-grade 1. Another appearance is that of a small volume of VUR reaching the renal pelvis with minimal or no visualization of the ureter (Fig. 13.5). This appearance corresponds to radiographic grades II or III, as it is not possible by the radionuclide technique to assess finely the diameter of the ureter and the anatomy of the pelvicaliceal system (RNC-grade 2). Finally, the radionuclide cystogram may reveal a large volume of reflux reaching a dilated pelvicaliceal system with definite or marked dilatation and even elongation and tortuosity of the ureter corresponding in appearance to radiographic grades IV and V (RNC-grade 3) (Figs. 13.6 and 13.7). Comparing the five VCUG grades of reflux with the three grade of reflux severity on RNC can be difficult, because of the technical differences between these two methods. This may be of particular concern when trying to compare the VCUG and RNC findings in the same patient to determine if reflux severity has changed over time.

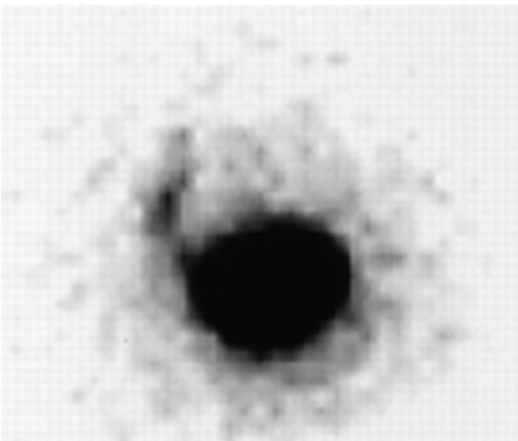


Fig. 13.4 Distal left vesicoureteric reflux, RNC severity grade 1. Reflux is limited to the left distal ureter without reaching the renal pelvis

Variability of Low-Grade Vesicoureteric Reflux

Vesicoureteric reflux is not a constant phenomenon. Low-grade VUR may vary from examination to examination. In our observation, using RNC, VUR varies also with bladder volume, voiding or filling, patient position, and level of anxiety. Reflux may be present during most of the filling and voiding phases of the radionuclide cystogram, or it may be intermittent (Fig. 13.8) [21, 22]. Therefore, it is

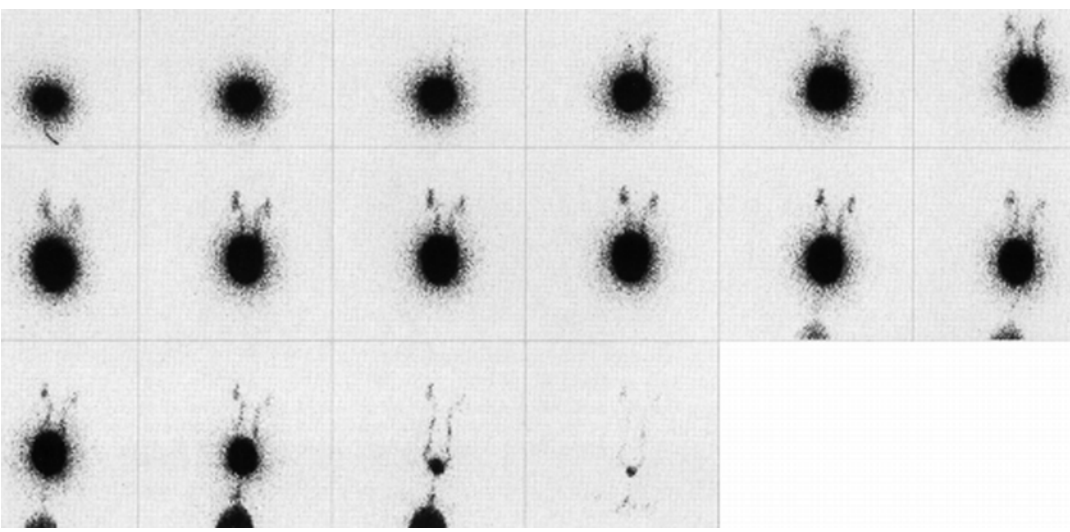


Fig. 13.5 Bilateral vesicoureteric reflux, RNC severity grade 2. Reflux reaches both renal pelves and persists during the filling and voiding phases of the RNC. At the end of voiding, a significant amount of tracer has drained out of the renal pelves, ureters, and bladder

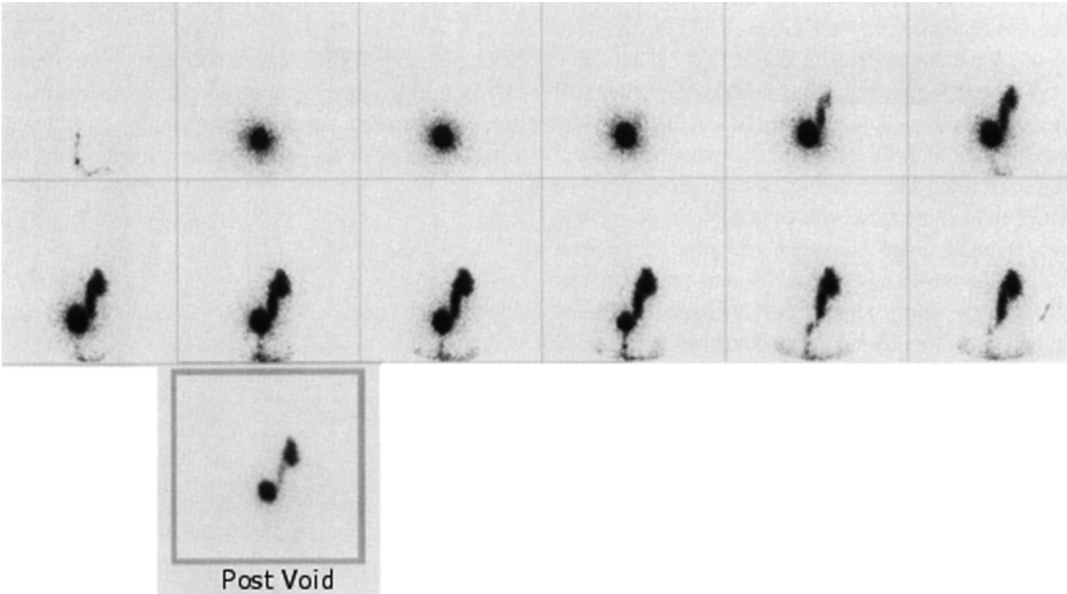


Fig. 13.6 Severe unilateral vesicoureteric reflux, RNC severity grade 3. Reflux is visualized in a dilated right ureter and renal pelvis. A postvoid image reveals significant retention of tracer in the renal pelvicaliceal system and ureter with secondary filling of the bladder

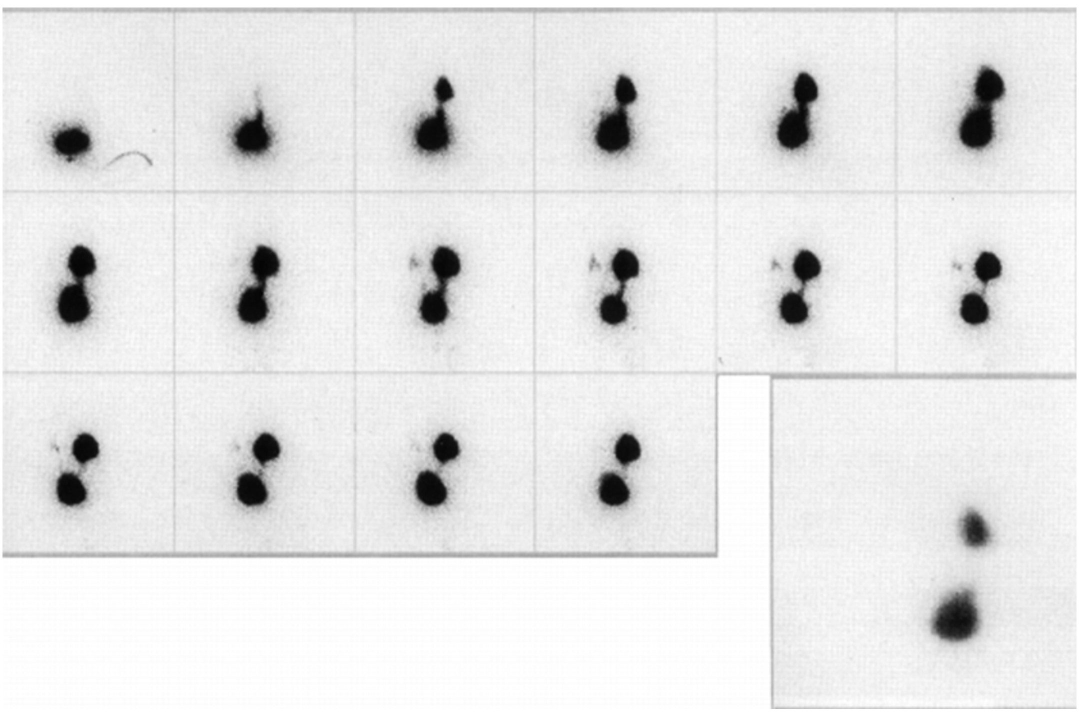


Fig. 13.7 Severe right vesicoureteric reflux (RNC severity grade 3) and mild to moderate left vesicoureteric reflux (RNC grade 2). Right reflux appears early at low bladder volume and persists during the entire examination. A postvoid image (*bottom right*) reveals secondary bladder filling and significant retention of tracer in the right renal pelvis. In addition, there is mild to moderate left vesicoureteric reflux reaching the renal pelvis. Left reflux occurs at higher bladder volumes, is intermittent, and drains rather rapidly even during bladder filling

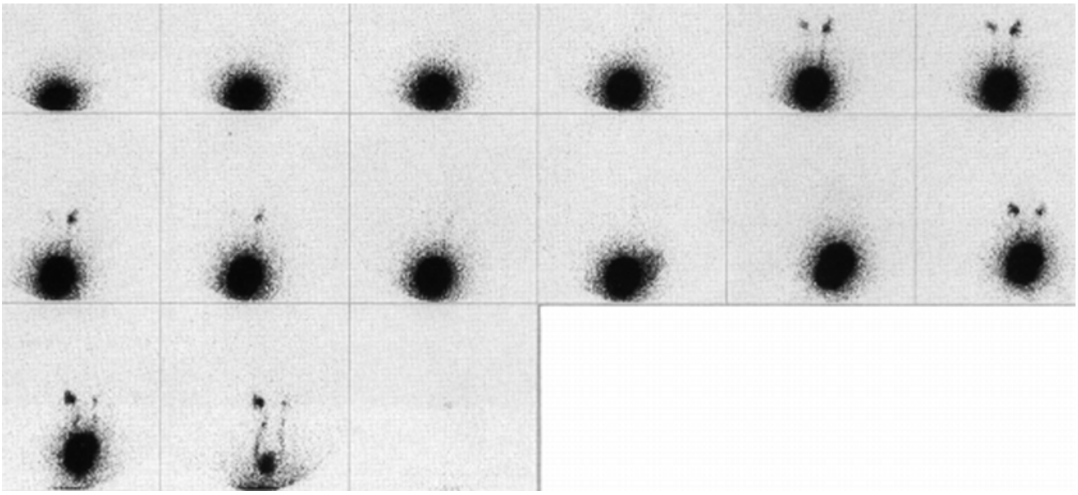


Fig. 13.8 Intermittent bilateral vesicoureteric reflux. Mild to moderate reflux appears almost simultaneously during the mid-filling phase in both ureters and renal pelves. During the mid- to late filling phase, reflux subsides temporarily in both sides and reappears during the late filling and voiding phases

clear that a single normal examination may not sufficient to ensure that VUR has resolved. Serial cystograms over several (6–12) months should provide greater assurance of complete cessation of reflux [23]. We have evaluated 480 ureters from 240 patients on two separate occasions when patients underwent RNC. The period between observations averaged 13 months (3 months to 3.7 years). None of the patients had prior surgery, neurogenic bladder, or other anatomic abnormality. This study revealed that 85 % of the ureters showed either no change (55 %) or decrease (30 %) in reflux severity. However, 15 % revealed an apparent worsening in reflux severity (9 %), or reflux was detected only on the second RNC (6 %). Two-stage RNC has also shown the variable nature of VUR [24, 25]. Treatment programs for VUR, therefore, should take into account the variability of low-grade reflux.

Spontaneous Cessation of Reflux

VUR frequently resolves with growth and maturation of the urinary tract. Spontaneous cessation of reflux was reported in approximately 71 % of children and 79 % of ureters studied by Normand and Smellie [26] in 1979. The most important factor in the resolution of VUR seemed to be the apparent diameter of the ureter at the time of diagnosis. Resolution of VUR took place in 85 % of ureters of normal caliber but in only 41 % of dilated ureters. In addition, these authors reported that 65 % of ureters associated with scarred kidneys also ceased to reflux spontaneously.

Treatment

Traditionally, patients with low-grade reflux have been treated with a regimen of long-term antibiotic prophylaxis. With severe reflux, spontaneous resolution of reflux can occur but is less likely. Continuous antibiotic therapy may be given to these patients provided their urine remains sterile, frequent urine cultures are performed, and that serial evaluation for reflux is carried out. This routine requires careful compliance by the patient and parents. Patients with peristent reflux, requiring prolonged antibiotic prophylaxis, febrile urinary infection despite prophylaxis, or severe reflux may be offered surgical correction of the vesicoureteral reflux.

Surgical treatment of VUR has a high degree of success in experienced hands [27, 28], offers an immediate correction of the anatomic problem, and reduces the risk of pyelonephritis. Neither medical nor surgical treatment, however, seems to offer a clear advantage related to subsequent development of hypertension or impairment of renal growth. Whichever form of therapy is chosen, long-term follow-up and observation are essential to assess the patient's progress and the presence of complicating factors, such as residual VUR, pyelonephritis, new scarring, hypertension, or renal dysfunction.

Radionuclide Cystography

Indications

Radionuclide cystography has four principal indications (Table 13.1) [1]. Because of its safety, high sensitivity, and minimal radiation exposure, RNC can be an ideal method for the initial diagnosis of VUR in some patients. For example, RNC can be an appropriate test in an older girl in whom there is less concern for urethral obstruction or anatomic abnormalities of the urinary tract. However, for younger children, most clinicians prefer to use VCUG for the first evaluation of the urinary tract, as it will provide more anatomic detail and better visualization of the urethra. Radionuclide cystography is indicated for the follow-up of patients who have been diagnosed previously with VUR and are receiving long-term prophylactic antibiotic therapy. Patients undergoing this type of treatment are typically monitored for reflux every 12–24 months. RNC also can be used for follow-up evaluation of patients found to have VUR during the evaluation of persistent prenatal hydronephrosis [29]. Radionuclide cystography is an effective technique for evaluating the results of surgical repair of VUR. In addition, and because of the low radiation dose and high sensitivity, RNC is a useful method for the evaluation of siblings for familial reflux [7–12].

Table 13.1 Indications for radionuclide cystography

Initial diagnosis of vesicoureteric reflux (VUR)
Follow-up of previously diagnosed VUR to assess for spontaneous resolution
Assessment of antireflux surgery
Diagnosis of familial VUR

Methods

There are two principal nuclear medicine methods to diagnose VUR: direct RNC and indirect radionuclide cystography (IRC). The direct method, which is by far the most common approach, requires bladder catheterization to introduce the radionuclide into the bladder in a retrograde fashion. Indirect radionuclide cystography does not require catheterization. Studies comparing RNC with IRC have suggested that RNC is more sensitive than IRC [30–32]. However, RNC is an invasive technique, so IRC may still have a role in the diagnosis of VUR in cooperative patients and in those who refuse catheterization [33]. Indirect radionuclide cystography requires that the patient refrain from voiding until the time of examination. Increased urinary output caused by recent administration of a diuretic (e.g., furosemide) or an intravenous contrast agent for urography or overhydration can interfere with the detection of VUR. Therefore, cystography should be performed first, or one should wait 1 day after administration of these agents.

Patient Preparation

The same patient preparation applies for both direct RNC and IRC. A complete explanation of the procedure should be given to the patient and parents. When done with patience and understanding, such a conversation can reduce anxiety before the examination. In addition, we find it helpful to hand out or mail a brochure with information and instructions for the RNC [21, 34]. We do not use sedation for RNC in the vast majority of the patients. The patient is instructed to void in the bathroom before the examination if possible and then to lie supine on the examination table for the study (see below).

Direct Radionuclide Cystography

Radionuclide cystography can detect small volumes of reflux, as little as 0.2 mL at 2 cm from the projected edge of the bladder [22]. RNC is indeed a stress test of the ureterovesical junction, with the bladder being filled in a retrograde fashion with a fluid at a higher rate than is natural. The radiation exposure to the patient with RNC is low, with a gonadal absorbed radiation dose of less than 0.03 mGy (3 mrad). Radionuclide cystography is highly sensitive, and the operator has greater control of the procedure than with IRC. Patients of all ages can be examined. As part of the procedure, a urine sample under aseptic conditions is obtained for culture.

Radiopharmaceutical

Technetium-99m (^{99m}Tc) as pertechnetate is used. The usual administered dose is 1 mCi (37 MBq). Alternative radiopharmaceuticals include ^{99m}Tc-labeled sulfur colloid and ^{99m}Tc-DTPA. Technetium-99m as pertechnetate should not be used in patients who have undergone bladder augmentation with gastric or intestinal mucosa. In these patients, ^{99m}Tc-pertechnetate may be absorbed into the circulation and interfere with detection of mild vesicoureteral reflux [35].

Equipment and Recording

The examination table is covered with plastic-lined absorbent paper to contain any spilled tracer and to reduce contamination of the table. A gamma scintillation camera system equipped with a high-resolution collimator is used. In our practice, the RNC is recorded as a series of 10-s frames in a 128 × 128 matrix format for the duration of the filling and voiding phases of the study. Postvoid images are obtained if the patient is not able to empty the bladder while on the imaging table.

Catheterization

Sterile urethral catheterization trays prepared for each study contain the following items: three small containers, cotton, and a sterile towel with a central opening. Other materials needed include antiseptic solution (PROVON Antimicrobial Lotion Soap, GOJO Industries, Inc., Akron, OH), sterile water, lidocaine anesthetic jelly, and a 10-mL syringe with a blunt, tapered adapter ("fistula tip"). Catheters of two sizes are used: a 2.6-mm-diameter catheter (French 8) for most patients and a 1.5-mm-diameter catheter (French 5) for infants.

The success of the examination depends to a great extent on careful catheterization technique. If necessary, a parent or aide assists in immobilizing the patient, who lies supine and is encouraged to relax. The so-called frog position is useful in catheterizing females. The periurethral area in females and the glans penis in males is carefully cleansed with antiseptic solution and sterile water warmed to body temperature before use. The catheter is lubricated with the anesthetic jelly to facilitate a smooth insertion. Using a bright spotlight, the female urethral orifice must be clearly identified before attempting catheterization. The catheter should be introduced easily in one motion, without hesitation. Any additional contact with the area surrounding the urethral orifice should be avoided because it causes discomfort. This point cannot be emphasized enough, because a child who has had a bad first experience with this procedure is not likely to cooperate in the future.

In boys, the urethra is anesthetized. The penis is held with one hand, while lidocaine jelly (5–10 mL) is slowly injected into the urethra using the blunt adapter. Slow and deep breathing helps to relax the sphincter and allows anesthesia of the entire urethra. Slightly squeezing the anterior portion of the penis for a minute or so prevents the lidocaine from draining out. The catheter is then gently and continuously introduced into the bladder. Encourage the patient to breathe deeply and attempt to void, which may relax the sphincter. If the sphincter remains closed, the catheter should be kept under continuous and mild pressure against it. In most cases, the catheter eventually glides through the sphincter.

Do not try to overcome a closed or spastic sphincter by repeated back-and-forth motions of the catheter as it may result in urethral injury. In the rare instance when it is necessary to repeat

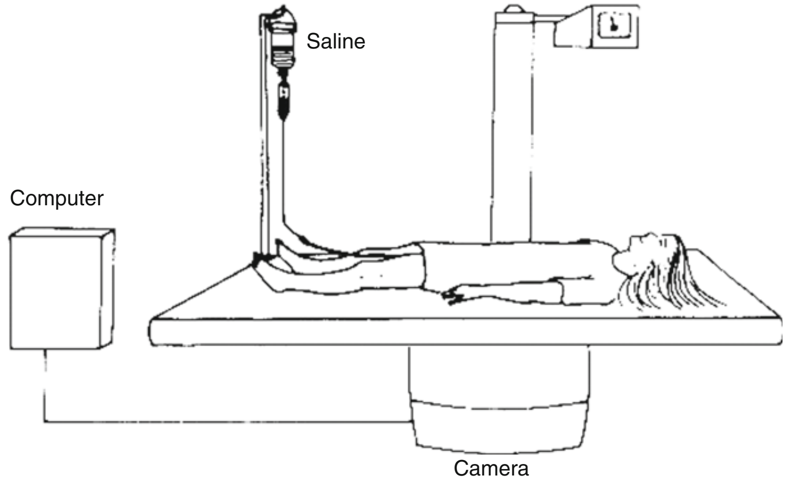


Fig. 13.9 Method of direct radionuclide cystography

the urethral anesthesia, a second attempt at catheterization is almost always successful.

Once the catheter has been advanced beyond the sphincter, most children cooperate. The residual bladder volume is then measured. The catheter is fixed with adhesive surgical tape to the inner thigh in girls and to the dorsal shaft of the penis in boys. Leaving the catheter in place until the end of the study allows for a repeat examination in case of failure, as well as for additional filling of the bladder if needed. In most cases, however, the catheter is removed gently before the patient voids. Some investigators have suggested direct RNC by direct percutaneous administration rather than bladder catheterization [36]. We have not employed this approach.

Filling and Voiding

The child is encouraged to lie quietly on the table. A calm environment and dim room lighting during the procedure often have a quieting effect. Many patients (and parents) find that watching a small ceiling-mounted TV while the study is in progress greatly helps reduce anxiety and makes the time pass more quickly.

The tracer is administered directly into the patient's bladder via the catheter (For computerized radionuclide cystography (CRVC), the radiopharmaceutical is mixed with the saline in the bottle and infused into the bladder [see section "Computerized Radionuclide Cystography", following]). A bag of 500 mL of normal saline (or irrigating solution) is suspended 70–90 cm above the bladder and connected to the catheter (Fig. 13.9). Gravity allows the saline solution to drain freely into the bladder. In our practice, we examine most patients in the supine position to more easily control the examination. However, the RNC can be performed in the sitting or semi-recumbent position if so desired.

While the bladder is filling, the operator monitors the entire examination on the computer monitor. The end of the filling phase is usually indicated by a bladder volume appropriate for the patient's age (see below) or a reduction or cessation of the infusate's rate of flow. When the bladder is filled to its capacity, voiding is usually initiated without delay. Careful and complete collection of the voided fluid is necessary for quantitation (see "Computerized Radionuclide Cystography" section below). We use a plastic urinal for both girls and boys. In girls its lower border is gently pressed against the perineum and inner thighs. If patients cannot void in the supine position, they are asked to try voiding in the sitting position.

The technologist or physician conducting the study should record the following: residual bladder volume, the fact that a urine sample was obtained under aseptic conditions for culture, any problems during the catheterization or the procedure, and voided volume. The data can be entered

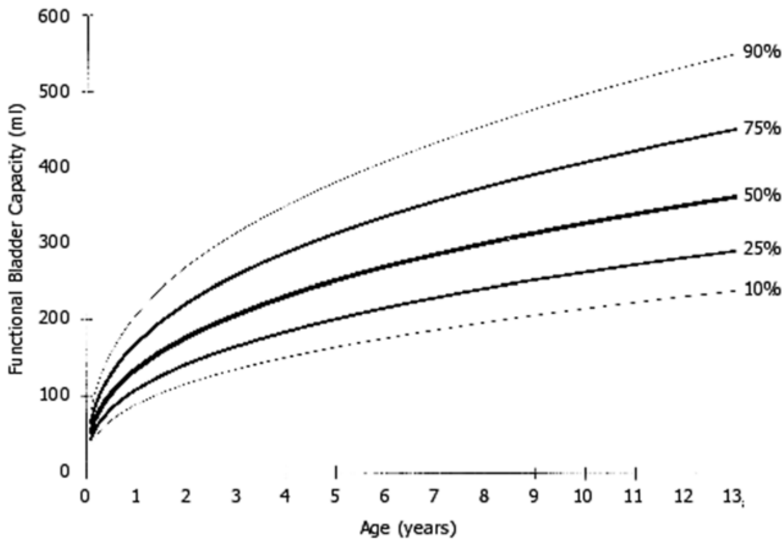


Fig. 13.10 Functional bladder capacity as a function of age in children less than 13 years of age

directly on the computer to be included within the diagnostic report.

Functional Bladder Capacity

Knowledge of the expected functional bladder capacity is useful for evaluation of VUR in children. However, a priori prediction of bladder capacity in children is difficult. Subjective criteria of complete bladder filling produced by the patient (toes curling upward, jiggling leg movements, complaints of urgency) should be noted, but their value may be unreliable.

Although bladder capacity generally increases with age and maturation, its variability at a given age or in a given patient may correspond to 100 % or more of the mean volume. Influences operating at the time of examination may cause the functional bladder capacity to be different from the actual capacity. Mechanical factors, such as rapid filling of the bladder, irritation from the catheter, or low temperature of the instilled fluid, can induce high bladder tonus and thus lower bladder capacity. Apprehension may provoke the same response. Uninhibited bladder contractions related to irritability from severe inflammation characteristically cause intermittent pain and urgency and tend to keep bladder capacity low. In most of the children with urinary tract infection (UTI) bladder capacity does not seem to be affected [21].

Information about bladder capacity on previous studies, mean values, and observation of the infusion flow rate should aid the operator in filling the patient's bladder to its approximate functional capacity. Several studies have addressed bladder capacity as a function of age in children, but published studies have included fewer than 250 observations [22, 37–40]. Those reports have indicated a linear relationship between age and functional bladder capacity. The following formula has been suggested: [37] bladder capacity (ounces) = age (years) plus 2. In addition, for children up to 1 year of age, a linear regression has been suggested: [38] capacity (mL) = [7.0 × weight (kg)] − 1.2. However, our experience using direct RNC suggests that this relationship is not linear [22].

We have reviewed the functional bladder capacities for more than 4,000 RNC examinations in children under 13 years of age. The relationship of functional bladder capacity and age seems to be nonlinear, and it can be described by a power model: $Y = \beta_0 X^{\beta 1}$, where Y is the estimated bladder capacity, β_o is the volume (constant), X is the age, and $^{\beta 1}$ is the slope power (Fig. 13.10) [41].

Analysis of Radionuclide Cystography

In routine practice, analysis of RNC is visual. The RNC should be viewed whenever possible on cinematic display, and the interpreter should be able to vary the playback speed and the contrast of the dynamic image set. With most low-grade reflux, the volume and amount of activity of refluxed tracer is much smaller than the activity within the bladder, so reflux could be missed if no contrast enhancement is used. No single approach covers all cases. Generally, it is useful to vary the upper threshold in the range between 5 and 15 % of the maximum level of activity in the image. Evaluation of the RNC with a series of static images is generally effective; however, evaluation on cinematic display is strongly recommended to achieve a higher diagnostic yield. Even with patient motion, dynamic evaluation enables the operator to distinguish scatter from minimal reflux better than on serial static images. Motion correction helps in the assessment of RNC where the patient has moved during the examination.

On occasion, time-activity curves from regions of interest over the renal, ureteral, and vesical regions may be utilized for quantitative evaluation of reflux, bladder volumes, and voiding flow rates with RNC (See following discussion of computerized voiding cystography). Meticulous attention to technique and complete avoidance of patient motion are mandatory for this approach [21].

Reporting Results

The RNC report should address at least the following information: voiding prior to the examination, residual bladder volume, the fact that a urine sample obtained under aseptic conditions was collected and sent to the laboratory for culture, problems with catheterization or the procedure, volume infused in the bladder, volume voided, presence and severity of reflux, and comparison with previous examinations (same, better, or worse). Most of our patients see a urologist after completion of RNC study; in our practice, the RNC report and images are immediately transmitted to the referring urologist.

Vesicoureteric Reflux in Radionuclide Cystography

An analysis of 135 consecutive radionuclide studies in our hospital revealed a 32 % incidence of VUR, usually RNC grades 1 or 2. Reflux was present in 47 % of the nonsurgical patients and in 11 % of the patients evaluated after surgery. It was unilateral in 60 % and bilateral in 40 %. Unilateral reflux occurred in the right and left ureters with equal frequency. In the 59 refluxing renal units, reflux occurred during filling and voiding in 80 %, whereas reflux present during voiding only was seen in 17 % of the ureters. These findings underscore the importance of examining the patient during voiding as well as during filling. The remaining 3 % of ureters refluxed during bladder filling only. Almost 80 % of those patients with reflux during filling and voiding refluxed 2–34 mL (average 7 mL) [21].

Patterns of Reflux

The ability to continuously monitor during RNC permits observation of several dynamic patterns of reflux. Continuously increasing reflux characteristically occurs during the early or mid-filling phase, supposedly through a patulous ureteral orifice that allows the bladder and ureter(s) to behave as a single chamber. This is the most severe reflux. Occurrence of reflux in this condition appears to be independent of intravesical pressure, which is usually low during the beginning of bladder filling [42].

Most commonly, VUR does not start until a certain bladder volume has been reached and then either continues to increase until the end of the filling phase or shows intermittent increases and decreases in volume. In some patients, however, there may be only one or few transient episodes of reflux during the filling or voiding phase (Figs. 13.11, 13.12 and 13.13). Some children who are unwilling or unable to void during the cystogram are asked to urinate in the bathroom, and a postvoid image is obtained. In some cases, the postvoid image shows the only evidence of VUR. Therefore, a postvoid image must be considered a routine part of the examination. In certain cases of bilateral reflux, one ureter can be

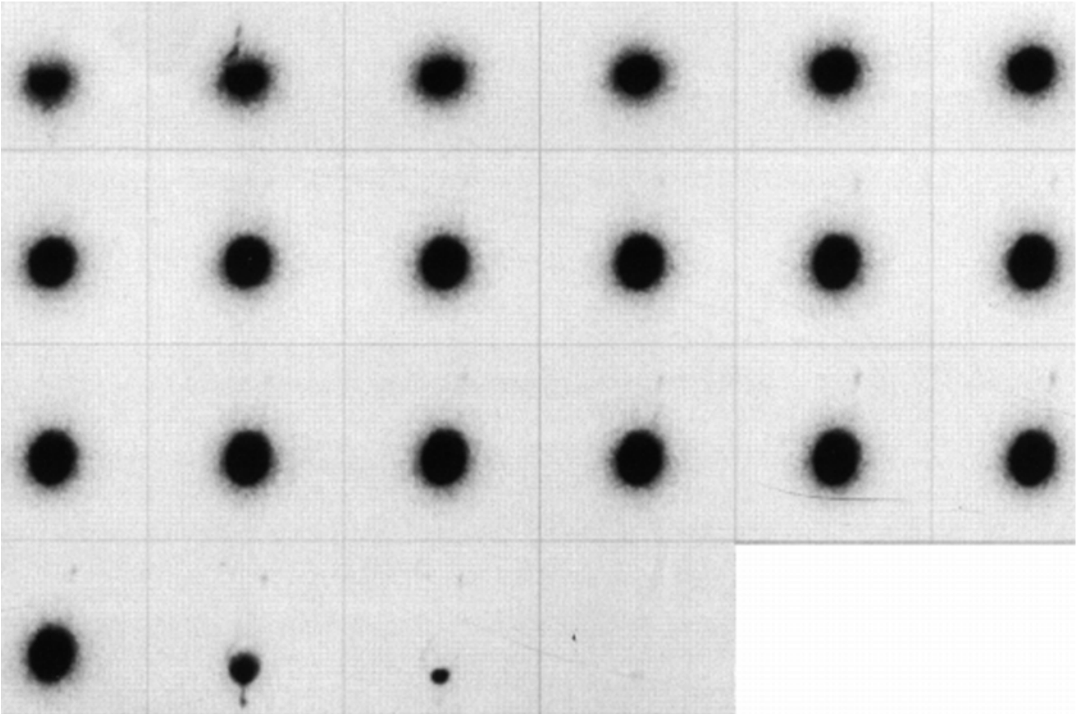


Fig. 13.11 Intermittent mild bilateral vesicoureteric reflux. Early (low bladder volume) left vesicoureteric reflux (VUR) subsides rapidly. As the RNC progresses toward the end of filling, there is mild bilateral VUR. An image obtained following the completion voiding reveals complete drainage of both ureteropelvicaliceal systems and the bladder

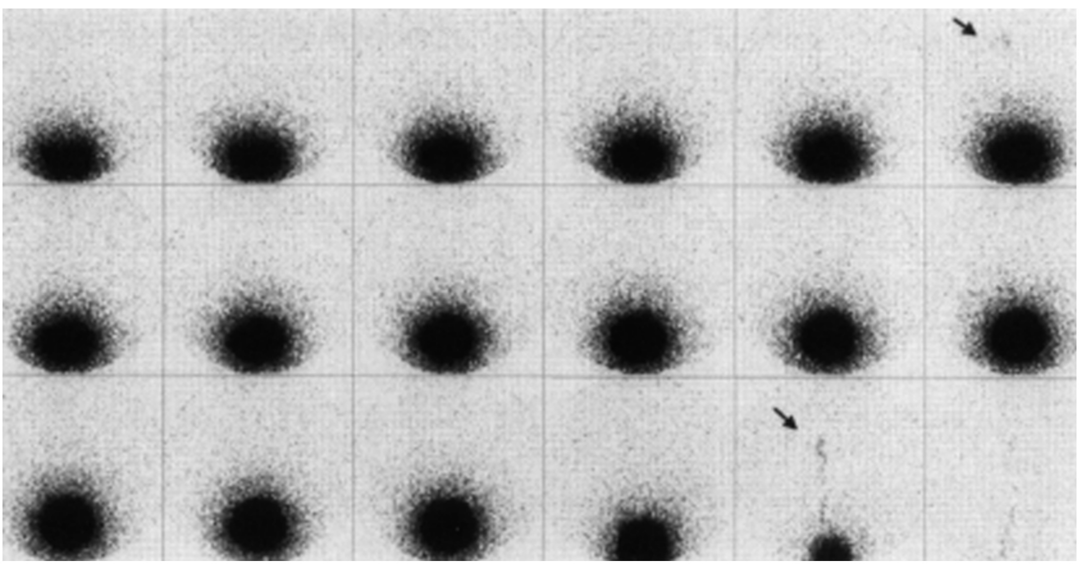


Fig. 13.12 Mild intermittent left vesicoureteric reflux. Left VUR is visualized briefly during the mid-filling phase; it then disappears completely and returns during the voiding phase (*arrows*)

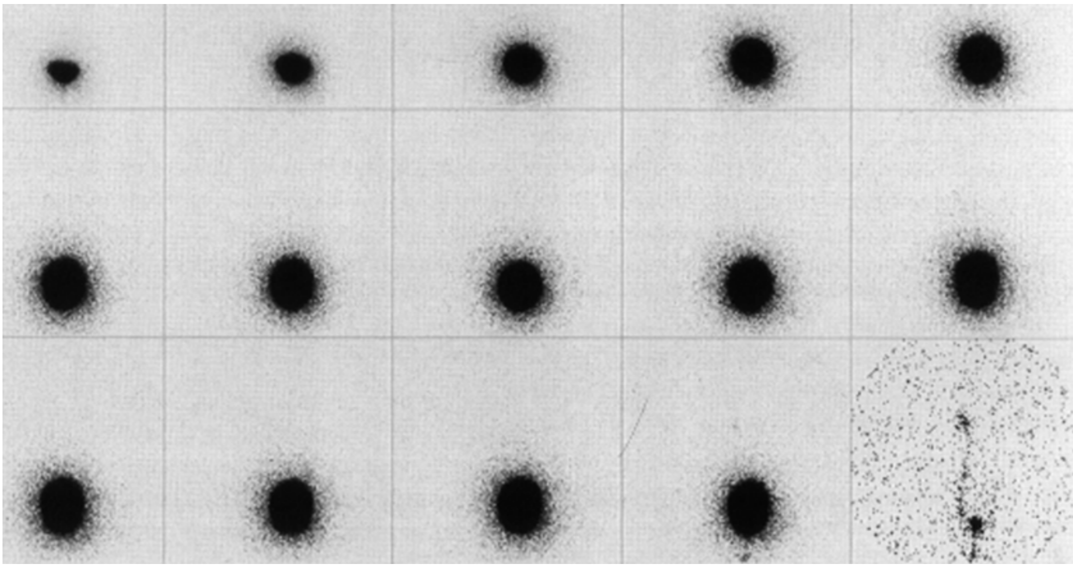


Fig. 13.13 Mild left vesicoureteric reflux. Reflux is seen only during voiding

seen to begin refluxing at a certain bladder volume, with reflux beginning in the contralateral ureter at a greater bladder volume.

If reflux has occurred during the filling phase, it may or may not increase in volume during the voiding phase, and in certain instances, it may decrease or disappear altogether during voiding. Refluxed fluid may continuously drain into the bladder immediately after completion of voiding, despite the fact that at this time intravesical pressure frequently reaches its maximum. Reflux, therefore, may have little to do with intravesical pressure and be more related to the degree of bladder filling and contraction.

Bladder Emptying and Voiding Flow Rate

The urine flow rate can be easily calculated with RNC [43, 44]. We calculated the voiding flow rates in 75 patients [21]. The average rate in 26 normal children was 10.2 mL/s [range 2.0–21.0 mL/s ± 4.5 standard deviation (SD)]. In 49 abnormal patients (reflux with or without infection or previous surgery), the voiding flow rates averaged 10.5 mL/s (range 1.4–31.0 mL/s ± 5.7 SD). In all 75 patients, the average voiding flow rate was 10.4 mL/s (range 1.4–31.0 mL/s ± 5.3 SD). The average voiding flow rate seemed to relate to the initial bladder volume and thus to age. The greater the initial bladder volume, the higher was the voiding flow rate. The presence of an indwelling catheter did not seem to reduce the voiding flow rate significantly. In patients with an indwelling catheter, it averaged 10.7 mL/s (range 2.0–31.0 mL/s), whereas in those without a catheter the average flow rate was 9.8 mL/s (range 1.4–25.0 mL/s). The voiding time was 10–116 s (average 35 s). With the exception of a few extreme values, the voiding time in normal patients is comparable to that in patients with reflux.

Children typically do not use abdominal straining during voiding [45]. When they do, the urinary flow either increases or decreases, probably reflecting whether the external sphincter is contracted along with the abdominal muscles [46]. Thus urging the child to strain in order to void may be counterproductive.

Residual Bladder Volume

Residual volumes measured by catheterization and RNC may or may not be the same, and in many instances, there is gross discrepancy between these two measurements for any number of

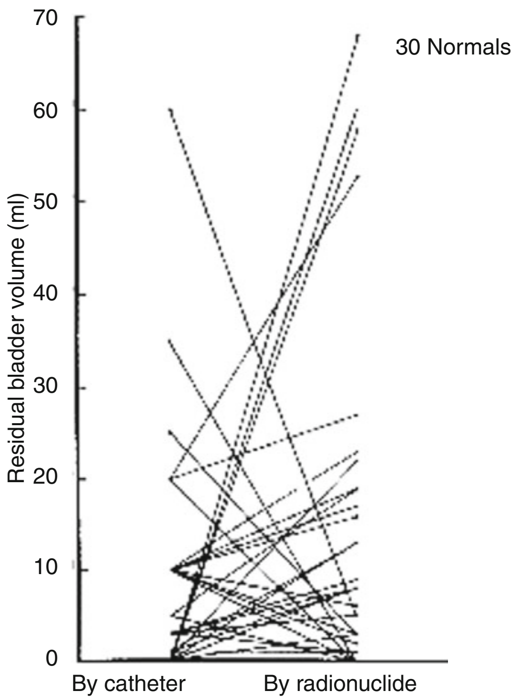


Fig. 13.14 Residual bladder volumes measured in the same patients by catheterization and by radionuclide cystography in 30 normal children

reasons (Fig. 13.14). For example, the patient may not adequately empty the bladder because of some underlying abnormality such as aberrant micturition, as in some cases of reflux or dysuria [47]. The bladder may not be properly drained because the tip of the catheter abuts the bladder wall, or the patient may simply be unwilling or unable to void because of the unnatural situation [48].

We have observed more complete emptying of the bladder in patients whose bladders were filled to a maximum or optimal volume during cystography. Apparently, high tonicity of the bladder wall induced adequate contraction and more complete emptying. A large residual volume in children at the beginning or end of the study does not necessarily mean that the patient has a significant abnormality. On the other hand, demonstration of an empty bladder is useful.

Urine Culture

We reviewed the results of urine culture in 113 consecutive children referred for radionuclide cystography. Urinary infection with *Escherichia coli* or *Streptococcus faecalis* was found in 11 % despite their history of continuous antibiotic treatment and careful follow-up by their physicians. Patients on antibiotic treatment and those who had undergone surgery showed a nearly equal incidence of urinary infection. Our experience agrees with that of other workers, suggesting that reflux and infection are independent of one another [49–53].

Dosimetry

For children undergoing RNC between ages 1 and 10, the absorbed radiation dose estimates for the bladder wall are 0.18–0.27 mGy and for ovaries 10–20 mGy. The testicular dose is less than the dose to the ovaries. The dose to the kidneys is estimated to be 0.02–0.04 mrad/mL of reflux per minute of residence in the collecting system. The estimated dose to the ureter in reflux is 13 mGy/min (1.3 mrad/min) [21, 54–56]. The dose to the ovaries is 100–200 times less with RNC than with conventional VCUG and 20–40 times less than pulsed fluoroscopy [21, 57, 58]. For these dose calculations, the residence time for the activity in the bladder is determined from the duration of the study in patients of various age groups and the empty bladder mass is estimated by extrapolation from data in adults, using growth curves [59].

Indirect Radionuclide Cystography

The principal advantages of IRC are that it can demonstrate reflux under physiologic conditions. It uses radiopharmaceuticals that, after intravenous injection, are rapidly eliminated in the urine and not retained in the renal parenchyma. Vesicoureteric reflux can be detected during voiding only. This technique has the advantage that it permits evaluation of renal function and urine drainage as well as detection of VUR. Indirect radionuclide cystography is less traumatic for the patient than RNC, physically and emotionally. It does not require catheterization and allows the bladder to be filled and emptied physiologically (Fig. 13.15). The minimal risk of induced infection is eliminated with IRC.

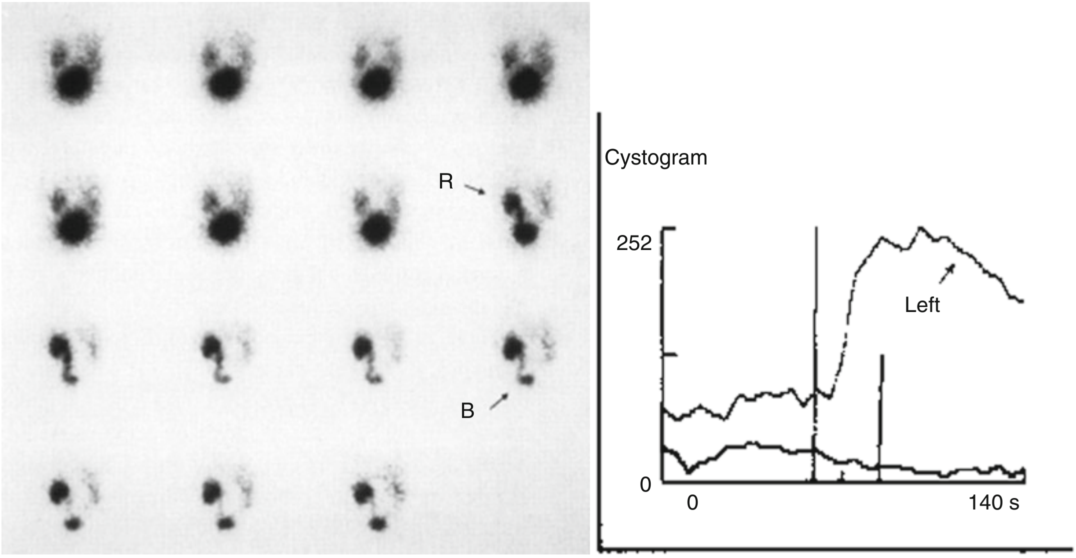


Fig. 13.15 Indirect radionuclide cystography (^{99m}Tc-MAG$_3$). *Left panel*: The bladder is filled with radiotracer. As the patient voids, there is left vesicoureteric reflux (*R*) and secondary bladder (*B*) filling. *Right panel*: The time-activity curve from a region of interest over the left kidney reveals a sharp increase coinciding with the reflux seen on the images (Courtesy of Dr. Isky Gordon, London, England)

However, IRC cannot detect VUR that occurs during the filling period only.

The patient can void in the usual position, so the competence of the vesicoureteral mechanism is tested under normal voiding pressures [33]. A relative disadvantage of IRC is that it requires complete patient cooperation. Clearly, IRC is not meant for newborns, infants, and those patients who cannot or will not cooperate. Another disadvantage of IRC is that it requires that the imaging room be available when the patient is ready to void.

Radiopharmaceuticals

The radiopharmaceuticals ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) or ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) are suitable agents for IRC. Technetium-99m-MAG3 is a better choice, as it has a higher extraction fraction with less soft-tissue background. The intravenous administered dose should be the same used as for dynamic renal scintigraphy.

Recording

Indirect radionuclide cystography should be preceded by a conventional dynamic renal scan in order to evaluate renal function and assess complete drainage of tracer from the kidneys. Ideally, no significant amount of tracer should be present in the renal regions prior to the start of the IRC, as VUR may be difficult to detect in the presence of residual tracer in the pelvicaliceal system. For the voiding phase, the patient is positioned in the sitting position with the gamma camera centered over the region of the bladder and kidneys. The patient voids into a urinal, a bedpan, or a specially made commode. Precautions to reduce contamination of the equipment and the room must be taken. Recording is begun when the patient is ready to void and continues until the end of voiding. Additional images may have to be obtained following voiding. The IRC is recorded using the same camera and computer acquisition parameters described under RNC (see above).

Analysis

Analysis of IRC is identical to that described above for RNC. The physician should review the IRC in a dynamic mode, varying the display rate and the image contrast.

Computerized Radionuclide Cystography

Computerized radionuclide voiding cystography (CRVC) is a refinement of RNC. It is a quantitative method and enables simultaneous measurement of bladder volumes and pressures. When using CRVC, the following parameters are obtained:

1. Volume of the bladder at the first occurrence of reflux and at the time of maximum reflux during filling and/or voiding
2. Maximum bladder volume (end of filling)
3. Volumes of reflux (initial, maximum, residual)
4. Residual bladder volume
5. Average voiding flow rate
6. Bladder pressures

Intravesical Pressure

With CRVC, it is possible to simultaneously record the radionuclide cystogram and the intravesical pressures. Using a double-lumen catheter, one channel is used for infusion and the other is connected to a pressure transducer. We use a 3-mm-diameter double-lumen catheter (French 9). The pressure transducer output is connected through an analog-to-digital converter to the computer. Time-activity and time-pressure curves can then be displayed simultaneously [21, 60, 61].

In a study in our institution aimed at establishing normal and abnormal ranges of intravesical pressure, measurements during RNC were obtained for 40 patients. There were 16 normal children, 15 with reflux, and nine who had previous surgery. In the normal children maximum intravesical pressures during filling were 15–80 cm H_2O (average 42 cm H_2O) and during voiding or postvoiding 24–136 cm H_2O (average 78 cm H_2O). There was no significant difference between the normal children, patients with reflux, and those who had prior reimplants. In all these groups, the initial voiding pressure was always slightly higher than the maximum filling pressure. Intravesical pressures decreased with increasing bladder volume. During filling of the bladder, the intravesical pressure showed a continuous increase until full bladder capacity was reached. Toward the end of voiding, a pressure peak that occurred after contraction characterized the pressure curve. In most instances, the highest recorded intravesical pressure was reached during this moment after contraction.

There is no clear evidence that intravesical pressure causes VUR [62]. A relationship between intravesical pressure and cortical renal damage in the absence of infection remains widely debated [63], although in patients with VUR there are alterations in renal blood flow during voiding [64]. Renal damage from pyelotubular backflow has also been considered [65]. It has been clearly demonstrated in children under 6 years of age, but mainly in infants, that massive reflux in the presence of urinary tract infection leads to renal damage [49, 62, 66–69].

Studies in rabbits reveal that renal blood flow decreases with acute increase of pressures in the pelvicaliceal system. This is reversible [70]. Intrarenal reflux seems to play an important role in the etiology of renal damage [71]. Because intravesical pressure is higher in younger than older children, it follows that intravesical pressure decreases with increasing bladder capacity. With renal damage occurring mainly in younger children, perhaps there is some relationship between intravesical pressure and reflux nephropathy. In the absence of a barrier at the ureterovesical junction, the upper urinary system and the bladder act as a single chamber. Studies in our laboratory seem to indicate that intravesical pressure is probably least important in terms of etiology, management, and prognosis of reflux provided that distal obstruction or neurogenic dysfunction is not present. Most of our patients exhibited reflux during filling at a relatively large bladder volume. The increasing bladder volume during the cystogram probably influences the anatomy and competence of the ureterovesical junction more than the increase in pressure.

In the growing child, maturation of the ureterovesical junction probably implies not only lengthening of the intravesical ureter but also strengthening of the specific musculature related to the ureterovesical junction. Therefore decreasing occurrence of reflux with age is to be expected [72–74]. Controversy still exists about maturation of the ureterovesical junction [53, 75]. Reflux only during voiding may be related to the changing anatomic condition of the ureterovesical junction during bladder contraction. The intravesical pressure at the initiation of voiding is not significantly higher than at the end of filling. Reflux that occurs at low bladder volume is more damaging [76].

Analysis

With CRVC, the sequential images of the cystogram are displayed on the computer monitor and evaluated visually (see above). If reflux is present, regions of interest (ROIs) are drawn over the kidneys and bladder. In addition, another region near the bladder is selected to correct for background scatter.

It is important to determine if patient motion occurred during the study because it invalidates any attempts at quantitation. Motion correction should be applied. Time-activity curves are calculated for each ROI.

To obtain and estimate the volumes of reflux, bladder capacity, and residual capacity, a relation between activity and volume is obtained. Assuming that attenuation of the gamma rays is constant, that the radioisotope is well mixed with the solution of saline, and that a negligible amount of urine is produced by the kidneys during the study, the counts recorded are proportional to the volume(s):

$$V = RC \qquad (13.1)$$

where V is volume, R is a constant, and C is counts. Note that 0 counts represents zero volume. The constant R is calculated by relating the voided volume to the drop in total vesical counts during the voiding phase of the study. At the beginning of the voiding phase, the volume is V_0 and the counts are C_0. At the end of the voiding phase, the volume is V_e and the counts C_e. Substituting these values into Eq. 13.1 yields:

$$V_0 = RC_0 \qquad (13.2)$$

$$V_e = RC_e \qquad (13.3)$$

Subtracting Eq. 13.3 from Eq. 13.2 yields:

$$R = \frac{V_0 - V_e}{C_0 - C_e} = \frac{V}{C} = \frac{\text{Change in volume}}{\text{Change in counts}} \qquad (13.4)$$

Once the ratios are calculated, it is easy to obtain any volume of interest for any particular time of the study (e.g., maximum volume of reflux). One simply has to multiply the ratio R by the number of counts over a particular region at a given frame. After the counts in each region are converted to volumes, it is possible to calculate rates of flow. To obtain the average voiding flow rate, the count loss during voiding must be divided by the time of voiding and multiplied by the constant R.

$$\text{Average flow rate} = R = \frac{\Box V}{AT} \qquad (13.5)$$

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