Original Article

Estimation of Renal Functional Reserve in Children with Different Grades of Vesicoureteric Reflux

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Background: Vesicoureteric reflux (VUR) is one of the most common anomalies encountered in pediatric urology. The concept of renal functional reserve (RFR) as the ability of the kidney to increase glomerular filtration rate (GFR) following a protein load was introduced in the 1980s.

Aim: This study aims to evaluate RFR using $^{99}$Tc diethylenetriamine pentaacetic acid (DTPA) as the filtration agent for GFR estimation in children with VUR.

Materials and Methods: RFR was estimated in 53 children, of which 31 patients had unilateral VUR (Group I) and 22 patients had bilateral VUR (Group II), by subtracting baseline GFR from stimulated GFR following an intravenous protein load. GFR was determined by double compartment-2 sample method using $^{99}$Tc DTPA radioisotope as the filtration agent. Both the groups were further subgrouped into low-grade (IA, IIA) and high-grade VUR (IB, IIB).

Results: The RFR was significantly lower in unilateral high-grade VUR (Group IB) as compared to unilateral low-grade VUR (Group IA) ($P = 0.024$). RFR was significantly lower in bilateral high-grade VUR patients (IIB) as compared to unilateral low-grade VUR group (IA) ($P = 0.0226$). Furthermore, the stimulated GFR shows very strong correlation to baseline GFR in both major groups ($r = 0.9659$ and $P = 0.001$ in Group I and $r = 0.9856$ and $P = 0.001$ in Group II) concluding that the baseline GFR and the stimulated GFR increase or decrease in tandem in both the groups.

Conclusion: The RFR is impaired in children with both unilateral high-grade VUR and bilateral high-grade VUR while it is relatively preserved in unilateral low-grade VUR and bilateral low-grade VUR.

Keywords: $^{99}$Tc diethylenetriamine pentaacetic acid, glomerular filtration rate, renal functional reserve, vesicoureteric reflux

INTRODUCTION

Vesicoureteric reflux (VUR) is one of the most common anomalies encountered in pediatric urology. The primary impetus for diagnostic and therapeutic interventions for VUR during the last three decades was the clinical association of VUR and urinary tract infection (UTI) that leads to pyelonephritis, renal scarring, hypertension, and chronic renal insufficiency (reflux nephropathy). However, many clinical and experimental studies done to establish causal relationship between pathophysiologic components of VUR, UTI, and other clinical sequel have led to debate rather than a unifying consensus.

When the number of functioning nephrons are decreased by congenital anomaly, surgery, or disease, there is an increase in single nephron filtration rate which is postulated to be an adaptive hemodynamic response. This adaptive response called glomerular hyperfiltration contributes to the maintenance of normal body composition in a patient with decreased number of functioning nephrons. Brenner et al. hypothesized

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that glomerular hyperfiltration has a central role in accelerating glomerulosclerosis and destruction.

The concept of renal functional reserve (RFR) was given by Bosch et al.[2] RFR represents the ability of the kidney to increase its filtration capacity from a basal level to a maximal level following certain stimulation, the most commonly used in man being an acute protein load.[2] It is calculated by subtracting the baseline glomerular filtration rate (GFR) from the stimulated GFR. The extent of this functional recruitment could be useful to evaluate the prognosis and follow kidney function in patients with chronic renal disease even with normal GFR in basal state.[3] Since the ingestion of protein acutely elevates the GFR (probably through renal vasodilatation and consequent hyperfiltration), the degree to which glomerular filtration responds to stress (protein ingestion/intravenous amino acid infusion) would thus provide an early measure of renal damage in VUR. In humans, the absence of RFR may be equivalent of hyperfiltration since the available nephrons are already working at their maximal level.

Numerous studies in various pathologic conditions describe the relationship of RFR in diseased state with that of healthy state utilizing different methods. In a study by Jindal et al.[4] RFR was estimated in children with hydronephrosis and was compared with RFR of healthy controls. They concluded that RFR is preserved in children with hydronephrosis, but it is reduced in comparison to healthy children. No study till date has studied RFR in pediatric patients with VUR. The present study was undertaken with an aim to evaluate RFR using intravenous amino acid infusion as acute protein load and diethylenetriamine pentaacetic acid (99Tc DTPA) radioisotope as the filtration agent for GFR estimation in children with VUR.

**Materials and Methods**

This prospective study was undertaken in the Department of Pediatric Surgery in collaboration with Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi. Ethical clearance was obtained in accordance with the Declaration of Helsinki. Double compartment 2 plasma sample method using 99Tc DTPA radioisotope as the filtration agent was used to measure the GFR, as it is the best test currently available with minimal error and less influenced by ingestion of food containing creatinine.[5] Two groups of individuals were studied. Group I comprised of 31 individuals with unilateral VUR and Group II comprised of 22 individuals with bilateral VUR.

Group I: Thirty-one patients, age range of 26–144 months, with the diagnosis of unilateral VUR confirmed on micturating cystourethrography (MCU) were included in this group. These patients were again subgrouped into Group IA (18 patients) and Group IB (13 patients). Group IA comprised of individuals with unilateral low-grade VUR (Grade I, II, III). Group IB comprised of individuals with unilateral high-grade VUR (Grade IV and V).

Group II: Twenty-two patients, age range of 32–141 months, with the diagnosis of bilateral VUR confirmed on MCU were included in this group. These patients were again subgrouped into Group IIA (9 patients) and Group IIB (13 patients). Group IIA comprised of individuals with bilateral low-grade VUR (Grade I, II, III). Group IIB comprised of individuals with bilateral high-grade VUR (Grade IV and V). Any individual with low-grade VUR on one side and high-grade VUR on the other side was included in Group IIB.

All the individuals in Group I and II were called on a scheduled date for baseline GFR and again within a week of the baseline study, for the protein-stimulated study. For this, individuals were given an intravenous infusion of mixed aminoacid solution (Aminoven infant 10%, Fresnius Kabi India Pvt. Ltd.) in the dose of 150–200 mg/kg over 30 min and the individuals were then injected with intravenous radiopharmaceutical agent for estimation of stimulated GFR. The RFR was calculated by subtracting the baseline GFR from stimulated GFR. This study was used to establish RFR in individuals with unilateral VUR (Group I) and bilateral VUR (Group II). Additional information such as presence of any renal anomaly on ultrasonography, functioning of the kidneys, and scarring of the kidneys on DMSA scan were also collected in both the groups. The derived RFR in Group II was analyzed statistically with that of Group I.

**Laboratory methods**

Informed consent of the parents was taken, and the procedure was explained to the parents and the children who could understand. Children were kept on normal diet, and good hydration and any ongoing medication were stopped before the study. 99mTc DTPA activity (1–2 mCi) was loaded in a preweighted syringe for the study groups. A standard dose was prepared similarly, and the standard dose was diluted in 1 liter of water. The individuals were injected with the dose prepared for the study group taking care not to extravasate the dose and the injection time was noted. The needle of the dose injected was washed in 10 ml of water. The needle was kept in plastic tube for residual count (N), and the syringe was appropriately discarded. Venous blood, 2–3 ml, was taken in heparinized tubes at 60 and 180 min after injection of the radioisotope. The plasma was separated from the blood sample by
gravity separation method. One ml plasma from 60-min sample was labeled as \( P_1 \) and from the 180-min sample as \( P_2 \). One ml of standard (1:1000 dilutions) was taken in a separate tube. One ml needle wash was diluted in 9 ml of water and taken in a separate tube and labeled as \( W \). \( P_1, P_2, \) standard, wash \( (W) \), and needle count was taken in a well counter. GFR was calculated using following formula:

\[
GFR = \left[ \frac{D \ln \left( \frac{P_1}{P_2} \right)}{T_2 - T_1} \exp \left( T_1 \ln P_2 - T_2 \ln P_1 \right) \right]^{0.979} 
\]

\( D \) = dose in counts injected to patient
\( P_1 \) = 60 min plasma sample count
\( P_2 \) = 180 min plasma sample count
\( T_1 \) = 60 min
\( T_2 \) = 180 min

Dose “\( D \)” is calculated by the following formula:

\[
D = \frac{\text{count in standard} \times \text{dilution of standard} \times 1000 \times \text{weight of injection dose}}{\text{weight of standard dose}} - N \times (W = 100)
\]

\( N \) = Needle counts
\( W \) = Wash counts

After calculating actual GFR, it is normalized by body surface area (BSA)

Normalised GFR = \[
\frac{GFR \times 1.73}{\text{BSA}}
\]

BSA is calculated using DuBois and DuBois formula, which is calculated by the following equation:

\[
\text{BSA} = \text{Height (cm)}^{0.425} \times \text{Weight (kg)}^{0.725} \times 0.007184
\]

**Results**

Fifty-three children in age range from 26 to 144 months were included in this study. Of these, 31 were individuals with unilateral VUR (Group I) and 22 were individuals with bilateral VUR (Group II).

In Group I, 18 were male (58%) and 13 were female (42%). Age ranged from 26 to 144 months (mean ± SD = 80.9 ± 38.52). Unilateral VUR (Group IA) and 13 patients (42%) had unilateral high grade VUR (Group IB). Renal anomaly was seen in 7 patients (22.5%). Base line GFR ranged from 63 ml/min/m² to 133 ml/min/m² (mean ± SD = 92.87 ± 22.93). Stimulated GFR ranged from 63 ml/min/m² to 138 ml/min/m² (mean ± SD = 101.19 ± 22.65). RFR ranged from −4 ml/min/m² to 25 ml/min/m² (mean ± SD = 8.32 ± 5.58). Unilateral scarring was seen in 15 individuals (48.38%). Bilateral scarring was seen in 8 individuals (25.8%). 7 individuals (22.58%) had no scarring. Scarring status was not known in 1 patient.

In Group II, 14 were male (63.64%) and 8 were female (36.36%). Age ranged from 32 to 141 months (mean ± SD = 89.31 ± 23.03). 9 individuals (40.9%) in this group had unilateral low-grade VUR (Group IIA) and 13 individuals (59.1%) had bilateral high-grade VUR (Group IIB). Renal anomaly was seen only in 1 patient in this group. Baseline GFR ranged from 54 ml/min/m² to 129 ml/min/m² (mean ± SD = 89.31 ± 23.03). Stimulated GFR ranged from 63 ml/min/m² to 137 ml/min/m² (mean ± SD = 95.59 ± 22.61). RFR ranged from −3 ml/min/m² to 12 ml/min/m² (mean ± SD = 6.27 ± 3.89). Unilateral scarring was seen in 9 individuals (40.9%). Bilateral scarring was seen in 7 individuals (31.81%). There was no scarring in 5 individuals (22.72%) and status of scarring was not known in 1 individual.

There was no significant difference in age \( (P = 0.91) \) and sex \( (P = 0.683) \) of the two major groups. Baseline GFR between two groups was compared using unpaired Student’s t-test, and the difference was not statistically significant \( (P = 0.58) \). There was also no statistically significant difference between the stimulated GFR \( (P = 0.37) \) and RFR \( (P = 0.14) \) between the two groups [Tables 1 and 2].

When unilateral low-grade VUR (Group IA) was compared with unilateral high-grade VUR (Group IB), there was no statistically significant difference in age \( (P = 0.206) \) between the two groups. There was also no statistically significant difference in the baseline GFR \( (P = 0.238) \) and stimulated GFR \( (P = 0.072) \) between the two groups. However, there
Table 1: Comparison of various quantitative variables in Group I (unilateral vesicoureteric reflux) and Group II (bilateral vesicoureteric reflux)

| Variables      | Groups  | n  | Mean±SD   | Median (maximum-minimum) | P   |
|----------------|---------|----|-----------|--------------------------|-----|
| Age            | Group I | 31 | 82.00±35.82* | 82 (144-26)              | 0.91|
|                | Group II| 22 | 80.90±38.52* | 75.5 (141-32)            | 0.58|
| Baseline GFR   | Group I | 31 | 92.87±22.93* | 90 (133-60)              | 0.77|
|                | Group II| 22 | 89.31±23.03* | 96.5 (129-54)            | 0.37|
| Stimulated GFR | Group I | 31 | 101.19±22.65* | 97 (138-63)              | 0.23|
|                | Group II| 22 | 95.59±22.61* | 104 (137-63)            | 0.07|
| RFR            | Group I | 31 | 8.32±5.58*   | 8 (25-4)                 | 0.14|
|                | Group II| 22 | 6.27±3.89*   | 7 (12-3)                | 0.25|

*P value calculated. SD: Standard deviation, GFR: Glomerular filtration rate, RFR: Renal functional reserve

was significant difference in RFR between the two groups (P = 0.0240) [Table 3] signifying that there is impairment of RFR in unilateral high-grade VUR as compared to RFR in unilateral low-grade VUR.

When bilateral low-grade VUR (Group IIA) was compared with bilateral high-grade VUR (Group IIB), there was no statistically significant difference in age (P = 0.349), the baseline GFR (P = 0.419), stimulated GFR (P = 0.375), and RFR (P = 0.568) between the two groups [Table 4].

When unilateral low-grade VUR was compared with bilateral low-grade VUR, there was no statistical significance in RFR (P = 0.12), baseline GFR (P = 0.76), and stimulated GFR between the two groups (P = 0.484) [Table 5].

When unilateral low-grade VUR was compared with bilateral high-grade VUR, there was statistical significance in the RFR (P = 0.0226). There was no statistical significance in baseline GFR (P = 0.15) and stimulated GFR (P = 0.051) [Table 6], signifying that the RFR is impaired in bilateral high-grade VUR as compared to RFR in unilateral low-grade VUR.

As we compare the relationship of baseline GFR and the stimulated GFR in both groups, the stimulated GFR shows very strong correlation to baseline GFR in both groups (r = 0.9659 and P = 0.001 in Group I and r = 0.9856 and P = 0.001 in Group II). This means that baseline GFR and the stimulated GFR increase or decrease in tandem in both the groups [Figures 1 and 2].

**DISCUSSION**

Under normal circumstances, the resting GFR in healthy children varies physiologically between 75 and 139 ml/min/m². The mean baseline GFR in Group I (unilateral VUR) and Group II (bilateral VUR) was 90 and 96.5 ml/min/m², respectively. The mean stimulated GFR in Group I (unilateral VUR) and Group II (bilateral VUR) was 97 and 104 ml/min/m², respectively. Thus, the baseline GFR and stimulated GFR in both the groups in this study lie within the normal range. These values are consistent with that suggested by Jindal et al.,[4] Terwee et al.,[6] and Memoli et al.,[7] who studied GFR in normal individuals.

The mean RFR in our study (7.43 ± 5 ml/min/m²) was less than the study reported by
Table 3: Comparison of various quantitative variables in Group IA (low-grade unilateral vesicoureteric reflux) and Group IB (high-grade unilateral vesicoureteric reflux)

| Variables   | Groups   | n  | Mean±SD      | Median (maximum-minimum) | P  |
|-------------|----------|----|--------------|--------------------------|----|
| Age         | Group IA | 18 | 74.72±40.30  | 74 (137-26)*              | 0.206 |
|             | Group IB | 13 | 92.15±26.76  | 96 (144-49)*              |     |
| Baseline GFR| Group IA | 18 | 97.05±21.34* | 96.5 (130-64)             | 0.238 |
|             | Group IB | 13 | 87.07±24.64* | 81 (133-60)               |     |
| Stimulated GFR | Group IA | 18 | 107.38±20.92* | 113 (138-67)            | 0.072 |
|             | Group IB | 13 | 92.61±22.92* | 86 (133-63)               |     |
| RFR         | Group IA | 18 | 10.33±5.53   | 10 (25-2)*                | 0.0240 |
|             | Group IB | 13 | 5.53±4.48    | 6 (12-4)*                 |     |

*P value calculated. GFR: Glomerular filtration rate, RFR: Renal functional reserve, SD: Standard deviation

Table 4: Comparison of various quantitative variables in Group IIA (bilateral low grade vesicoureteric reflux) and Group IIB (bilateral high grade vesicoureteric reflux)

| Variables   | Groups   | n  | Mean±SD      | Median (maximum-minimum) | P  |
|-------------|----------|----|--------------|--------------------------|----|
| Age         | Group IIA | 9  | 85.88±33.41  | 87 (139-50)*             | 0.349 |
|             | Group IIB | 13 | 77.46±42.67  | 50 (141-32)*             |     |
| Baseline GFR| Group IIA | 9  | 94.22±26.25* | 97 (129-60)              | 0.419 |
|             | Group IIB | 13 | 85.92±20.94* | 86 (113-54)              |     |
| Stimulated GFR | Group IIA | 9  | 100.88±25.28* | 106 (137-69)          | 0.375 |
|             | Group IIB | 13 | 91.92±20.82* | 92 (122-63)              |     |
| RFR         | Group IIA | 9  | 6.66±4.21    | 8 (12-2)*                | 0.568 |
|             | Group IIB | 13 | 6.00±3.80    | 6 (11-3)*                |     |

*P value calculated. GFR: Glomerular filtration rate, RFR: Renal functional reserve, SD: Standard deviation

Jindal et al.[4] (17.10 ± 12.08 ml/min/m²) and De Santo et al.[8,9] (27 ± 4 ml/min/m², 39.7 ± 5.2 ml/min/m², 24 ± 0.9 ml/min/m², 20.1 ± 1.13 ml/min/m²) in four different studies done in normal children. This can be because of the method used by De Santo et al. for GFR estimation (Inulin clearance) and the different protein load in the form of beef steak served orally. The study that closely resembles our study in method of GFR estimation and RFR estimation is that of Jindal et al.[4] who estimated it in normal children and children with hydronephrosis. Nevertheless, the mean RFR estimated in our study is on the lower side of the normal range reported by Jindal.
The highest RFR estimated in our study was 25 ml/min/m². The individual in this case had unilateral low-grade VUR (Grade II). The highest RFR in unilateral high-grade VUR was 12 ml/min/m² which is lower as compared to RFR estimated in unilateral low-grade VUR. When the RFR in unilateral low-grade VUR (IA) and unilateral high-grade VUR (IB) was compared, the data were statistically significant (P = 0.0242), indicating that there is significant RFR impairment in case of unilateral high-grade VUR.

The highest RFR estimated in bilateral low-grade VUR (12 ml/min/m²) and bilateral high-grade VUR (11 ml/min/m²) were lower as compared to highest RFR estimated in unilateral low-grade VUR. However, when the RFR between unilateral low-grade VUR (IA) and bilateral low-grade VUR (IIA) was compared, there was no statistical significance (P = 0.12), indicating that the RFR in bilateral low-grade VUR is relatively preserved. When status of RFR in unilateral low-grade VUR (IA) was compared with RFR in bilateral high-grade VUR (IIB), the data were statistically significant (P = 0.0226), indicating impairment of RFR in bilateral high-grade VUR.

The above observations signify that as the grade of reflux increases and disease progresses to opposite side, more number of nephrons are recruited resulting in decreased RFR. Vallés and Cruzado evaluated the acute effect of oral protein load on GFR in 9 patients with bilateral high-grade VUR after surgical correction and compared the results with 9 children with repeated UTI without reflux and 6 healthy controls of similar age. They concluded that RFR was significantly impaired in patients with bilateral high-grade VUR, finding which is consistent with our observation in this study.

Almost in all the individuals, the stimulated GFR shows an increasing trend as compared to baseline GFR, but in case (unilateral high-grade VUR), it is equal to the baseline GFR, suggesting that in an already hyperfiltrated kidney, the acute protein load has very limited scope to increase the GFR. In 3 cases, the stimulated GFR shows a decrease as compared to baseline GFR, the cause of which is not known. It may be because of the fact that there are various other determinants of RFR, and lack of knowledge about these factors may contribute to these findings. Anastasio et al. had described the problems encountered in the evaluation of RFR in childhood. Of these, lack of knowledge on protein intake and sodium intake are the critical factors that determine the RFR.

Bosch et al. used creatinine clearance method for estimation of GFR. However, the use of creatinine clearance has many drawbacks in assessing GFR as shown by Laville et al. and Shemesh et al. who demonstrated inaccuracy of this method for determination of RFR after a meat meal in renal disease. Since DTPA is a glomerular agent excreted solely by the glomerulus and not affected by meat meal, we have used ⁹⁹mTc DTPA radiopharmaceuticals for estimating GFR in our study.

We have used intravenous aminoacid infusion as the protein load for determination of GFR in our study. This is because there is strong relationship between GFR and protein intake and it was difficult to ensure stipulated amount of protein through diet in our individuals.

In our study as we compared the relationship of baseline GFR and stimulated GFR, we found strong correlation between the two in both groups (Group I P = 0.001, r = 0.96) (Group II P = 0.001, r = 0.98). This means that the baseline GFR and stimulated GFR increase or decrease in tandem with each other. We also observed weak inverse correlation between baseline GFR and RFR in both the groups. Memoli et al. in their study has shown inverse relationship of RFR to baseline GFR. This inverse relationship seems to be lost in case of VUR (both unilateral and bilateral VUR).

Major limitation of this study lies in grouping of the patients into unilateral and bilateral VUR. This is because the grouping has been done on grade of reflux on MCU. In our collected data, we have documented renal scars on contralateral side of VUR, giving an indirect evidence of bilateral VUR in patients who have been grouped into unilateral VUR. Another limiting factor is the sample size in each of the individual groups. It is difficult to arrive at conclusion with small sample size. Nevertheless, the observation that RFR is significantly impaired in unilateral high-grade VUR and bilateral high-grade VUR and relatively preserved in unilateral low-grade VUR and bilateral low-grade VUR is a significant finding. It may also be possible to use RFR estimation in identifying which grade of VUR is a risk factor for progressive renal damage and for initiating therapeutic interventions.

**CONCLUSION**

The RFR is preserved in unilateral low-grade and bilateral low-grade VUR. The RFR is impaired in unilateral high-grade and bilateral high-grade VUR signifying the need for early intervention in high-grade VUR to prevent further damage to renal function. However, in view of limitations of the study already described, there is a need to perform this study in a larger cohort.
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Conflicts of interest
There are no conflicts of interest.

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