The role of renal function reserve estimation in children with hydronephrosis

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ABSTRACT

Background: Glomerular filtration rate (GFR) is the most widely used indicator of kidney function although it does not invariably reflect the functional status after renal injury. The concept of renal function reserve (RFR) as the ability of the kidney to increase GFR following a protein load was introduced in 1980s. In hydronephrotic children, the acute hemodynamic response to intravenous protein load can cause changes in renal function that are different from changes in normal controls. Materials and Methods: RFR was evaluated in 21 children with hydronephrosis (group I - study group) and in 20 healthy children (group II - control group) by subtracting the baseline GFR from the stimulated GFR following an intravenous protein load. GFR was determined by double compartment-2 plasma sample method using 99mTc DTPA (diethylenetriamine pentaacetic acid) radioisotope as the filtration agent. Results: The baseline GFR, stimulated GFR and RFR of hydronephrotic children (group I) was found to be significantly lower (P = 0.01, P = 0.001 and P = 0.03 respectively) as compared with healthy normal children (group II). The stimulated GFR shows a strong correlation with the baseline GFR in both the groups, but the RFR shows a high inverse correlation to the baseline GFR in controls and a very low correlation in study group. Conclusion: RFR is preserved in children with hydronephrosis, but it is reduced in comparison to healthy children. However, its clinical utility to unmask the severity of hydronephrosis is limited by the various limiting factors.

KEY WORDS: Glomerular filtration rate (GFR), hydronephrosis, intravenous amino acid load, renal function reserve (RFR)

INTRODUCTION

Hydronephrosis resulting from pelviureteric junction (PUJ) obstruction is one of the most enigmatic problems in children. There is a tremendous variability in the natural history of this condition. While some undergo progressive and often irreversible renal injury, others remain stable for long periods, or even improve with growth. When the numbers of functioning nephrons are decreased by congenital anomaly, surgery or disease, there is an increase in single nephron filtration rate; this is postulated to be an adaptive hemodynamic response.[1] This adaptive response, called glomerular hyperfiltration, contributes to the maintenance of homeostasis in a patient with decrease in the number of functioning nephrons. Pascual et al.[2] suggested that hyperfiltration developed as a primary phenomenon in PUJ obstruction and may have a fundamental role in progression to irreversible renal damage.

The concept of renal function reserve (RFR) was introduced by Bosch.[3] This represents the ability of the kidney to increase the glomerular filtration rate (GFR) from a resting value to a maximal one and is measured by the difference between resting and maximal GFR (filtration capacity of the kidney). The extent of this functional recruitment could be useful not only to evaluate the prognosis but also to serially follow kidney function in patients with chronic renal disease even when GFR is normal in the basal state.[4] The ingestion of protein acutely elevates the GFR, probably through renal vasodilatation and consequent hyperfiltration. The degree to which glomerular filtration responds to the stress of protein load would thus provide an early measure of RFR in PUJ obstruction.

This study was undertaken with an aim to evaluate RFR using intravenous infusion of amino acid to provide an acute protein load and 99mTc DTPA (diethylenetriamine
pentaacetic acid) radioisotope as the filtration agent for GFR estimation, both in healthy children and in patients with hydronephrosis.

MATeRIALS AND METHODS

This prospective study was undertaken in the Department of Pediatric Surgery in collaboration with the Department of Nuclear Medicine, at the All India Institute of Medical Sciences, New Delhi, from 2003 to 2005. We used the double compartment-2 plasma sample method to measure the GFR, as it is the best test currently available with minimal error and least influenced by ingestion of food containing preformed creatinine.[5]

Patients and controls: Two groups of subjects were studied. Group I comprised of 21 children with hydronephrosis (study patients) and Group II comprised of 20 healthy children (control group).

Group I (study group): Twenty-one patients with age range of 6 months to 12 years with the diagnosis of hydronephrosis confirmed on ultrasonography and renal dynamic scan were included in this group. Of the 21 cases in group I, 4 (19%) had bilateral hydronephrosis (group IA) and 17 (81%) had unilateral hydronephrosis (group IB). Of the 17 cases with unilateral hydronephrosis, 11 (64%) were left-sided and 6 (36%) cases were right-sided. The subjects were called on a scheduled date for a baseline GFR, and again within a week of the baseline study for the protein-stimulated study. For this, the subjects were given an intravenous infusion of mixed amino acid solution (Aminoven® Infant 10%; Fresenius Kabi India Pvt. Ltd.) in the dose of 150-200 mg/kg over 30 min. The infusion was started at the time of intravenous radiopharmaceutical dose injection. The RFR was calculated by subtracting the baseline GFR from the stimulated GFR. This study was used to establish the renal reserve in children with hydronephrosis.

Group II (control group): To estimate the RFR in normal healthy children, 20 children below the age of 12 years, who had normally functioning bilateral kidneys, confirmed on renal dynamic scan, were included. All these patients were subjected to one baseline and one protein-stimulated study as per the protocol described above for hydronephrotic children in the study group. The derived RFR was analyzed statistically with that of hydronephrotic children.

Laboratory methods: Informed consent of the parents was taken and the procedure was explained to the parents and the children who were able to understand. The children were kept on normal diet with good hydration, and any ongoing medication was stopped before the study. 99mTc DTPA activity (1-2 mCi) was loaded in a pre-weighted syringe for the study groups. A standard dose was prepared similarly and the standard dose was diluted in 1 l of water. The subjects in Group I and Group II were injected with the dose prepared for the study group taking care not to extravasate the dose and the injection time was noted down. The needle of the dose injected was washed in 10 ml of water. The needle was kept in a plastic tube for residual count (N) and the syringe was appropriately discarded. A venous blood sample (2-3 ml) was taken in a heparinized tube at 60 min and 180 min after injection of the radiopharmaceutical. The plasma was separated from the blood sample by gravity separation method. One milliliter plasma from the 1-h sample was labeled as P1 and from the 3-h sample was labeled as P2. One milliliter of standard (1:1000 dilutions) was taken in a separate tube. One milliliter needle wash was diluted in 9 ml of water and 1 ml of this diluted needle wash was taken in a separate test tube and labeled as W. P1, P2, standard, wash (W), and needle count (N) were taken in a well counter. GFR was calculated using the following formula:

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

where D = dose in counts injected to patient
P1 = 60 min plasma sample counts
P2 = 180 min plasma sample counts
T1 = 60 min
T2 = 180 min

Dose, D, is calculated by the following formula.

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

where N = needle counts
W = wash counts

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

Normalized GFR = \frac{GFR \times 1.73}{BSA}

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

Statistical analysis: All the data were entered in a Microsoft Excel spreadsheet and the data consistency was checked by double entry. Descriptive statistics were calculated for each variable using the Statistical Package
for Social Sciences (SPSS 11.5). The mean of each variable was compared by using unpaired Student’s ‘t’ test. Categorical variables were compared using Chi-squared test. A P-value of < 0.05 was considered statistically significant.

RESULTS

In group I, all the children were in the age range of 6 months to 12 years (mean ± SD = 3.669 ± 3.54); and in group II all the children were in the age range of 2 years to 12 years (mean ± SD = 4.90 ± 3.37). There is no significant difference between the groups in age and sex.

The baseline GFR (global GFR) in group I ranged from 58 to 122 ml/min/1.73 m² (mean ± SD = 89.95 ± 16.8) and in group II, it ranged from 75 to 139 ml/min/m² (mean ± SD = 105.50 ± 15.36). The difference between the baseline GFR of the two groups was found to be statistically significant (P = 0.01); children with hydronephrosis had a lower baseline GFR as compared to healthy normal children. The stimulated GFR (S GFR; filtration capacity of the kidney) in group I ranged from 70 to 123 ml/min/m² (mean ± SD 100.38 ± 17.15), and in group II it ranged from 95 to 139 ml/min/m² (mean ± SD 122.10 ± 11.38). The filtration capacity of hydronephrotic children (group I) was found to be significantly lower than the controls (group II) (P = 0.001). The RFR in group I ranged from 4 to 37 ml/min/m² (mean ± SD = 10.43 ± 6.72) and in group II it ranged from -18 to 38 ml/min/m² (mean ± SD = 17.10 ± 12.08); this difference between the two groups was found to be statistically significant (P = 0.03). The details have been presented in Table 1.

The trends of renal reserve in the study group and controls are shown in [Figures 1-3]. There is a high degree of variability in the post-stimulation rise in GFR in the control group [Figure 1]; in some subjects, there is no rise in GFR following stimulation and in one subject, it even shows a fall in the GFR following stimulation. The trends of renal reserve in the study group are quite similar to the control group [Figures 2 and 3].

As we compare the relationship of baseline GFR, the stimulated GFR and RFR to age, the results show that baseline GFR, stimulated GFR and RFR are not age-

| Table 1: Comparison of various quantitative variables in group I (study group) and group II (control group) |
|---------------------------------------------|-----------------|-----------------|-----------------|
| Variable | Group I (n = 21) | Group II (n = 20) | P-value |
| Age | 3.69 ± 3.54 | 4.9 ± 3.37 | 0.27 |
| GFR | 89.95 ± 16.82 | 105.50 ± 15.36 | 0.01 |
| S-GFR | 100.38 ± 17.15 | 122.10 ± 11.38 | 0.001 |
| RFR | 10.43 ± 6.72 | 17.10 ± 12.08 | 0.03 |

Figure 1: Trends of renal reserve in control group

Figure 2: Trends of renal reserve in group I-A (bilateral hydronephrosis)

Figure 3: Trends of renal reserve in group I-B (unilateral hydronephrosis)
dependent. However, the stimulated GFR shows a very strong correlation with the baseline GFR in the study group \((r = 0.922, \ P = 0.001)\) and in the control group it shows a high correlation \((r = 0.643, \ P = 0.002)\) as shown in [Figure 4]. The RFR in the control group shows a high inverse correlation \((r = -0.650, \ P = 0.002)\) to the baseline GFR [Figure 5], but in the study group, there is a very low correlation between RFR and baseline GFR \((r = -0.152, \ P = 0.511)\). There is also a very low correlation between stimulated GFR and RFR in both the groups [Figure 6].

**DISCUSSION**

Under normal circumstances, the resting GFR in healthy children may vary between 85-140 ml/min/m², depending on the basal tone of glomerular arterioles. The highest GFR value in our normal subjects obtained by intravenous infusion of amino acid is consistent with that suggested by Terwee et al.\[6\] and Memoli et al.\[7\] (140 ml/min/m²). The stimulated GFR in healthy children shows an increasing trend as compared to baseline GFR as shown in [Figure 2]; but in two cases 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 and this is consistent with other studies.\[7\] However, in one case the stimulated GFR shows a decrease as compared with the baseline GFR of 126 ml/min/m²; on the basis of existing knowledge, this cannot be explained. It may be because of the fact that there are various other determinants of renal reserve and lack of knowledge about these factors may be contributory to this exceptional finding.

Anastasio et al.\[8\] had described the problems encountered in the evaluation of renal reserve in childhood. Of these, lack of knowledge on protein intake and sodium intake are the critical aspects as both of them are major determinants of renal reserve. Adding to these, other factors like information on blood pressure, heart rate, methods for starting/sustaining diuresis, urinary flow rate and number of blood samples has an impact on the evaluation of renal reserve.

The mean RFR in our study \((17.10 \pm 12.08 \text{ ml/min/m}²)\) is almost comparable to the study reported by De Santo et al.\[9,10\] \((27 + 4 \text{ ml/min/m}², 39.7 + 5.2 \text{ ml/min/m}², 24 + 0.9 \text{ ml/min/m}² \text{ and } 20.1 + 1.13 \text{ ml/min/m}² \text{ in four different studies.})\[7\] In the study by Molina et al.,\[11\] the mean value of RFR in school children \((60.2 \text{ ml/min/m}²)\) was higher than the level of 34 ml/min/m² reported in adults by Bosch et al.\[4\]. The discrepancy in the study by Molina et al.\[11\] may be due to overestimation of RFR because of the use of a single post-meal serum creatinine for both the pre-meal and post-meal creatinine clearance determination. It should be stressed that in the study by De Santo et al.,\[9\] there are many methodological problems that are related to sodium and protein intake as well as quantity and quality of protein load. Also, sodium intake, which is one of the determinants of renal hemodynamic response to meat meal,\[12\] has not been considered in most of their studies. Creatinine clearance was used by Bosch\[4\] and its use was validated by means of parallel studies with inulin. However, the use of creatinine clearance has many drawbacks in assessing GFR and RFR, specially in renal disease. After a meat meal, plasma creatinine concentration increases significantly as reported by Laville et al.\[13\] and Shomesh et al.\[14\] who showed the inaccuracy of this method for determination of renal reserve after a meat meal and in renal disease. Since DTPA is a glomerular agent excreted solely by the glomerulus and not affected by meat meal, we have.
used $^{99m}$Tc DTPA radiopharmaceutical for estimating GFR in our study.

Since there is a strong relationship between GFR and protein intake, all investigated subjects should have a record of the measure of protein intake. This was not possible in children who were investigated on an outpatient basis. Also, since the compliance in children is variable, it is difficult to ensure a stipulated amount of protein diet. Hence, in our study, we used intravenous amino acid infusion as the protein load for determination of RFR. It has been confirmed in many studies that the changes in renal hemodynamics after a meat meal are similar to that observed after intravenous administration of a mixture of amino acids.

In our results, we observed that in healthy children the RFR has a high inverse correlation to the resting GFR [Figure 5], which is consistent with the observation of Memoli et al.,[7] who had shown an inverse relationship of RFR to the baseline GFR. In the study group, however, the RFR has a low correlation to the baseline GFR. We also demonstrated that the resting GFR, stimulated GFR and RFR are not age dependent in either group. Filtration capacity (stimulated maximal GFR) has a high correlation with baseline GFR in the control group ($r = 0.643, P = 0.002$), and a strong correlation ($r = 0.922, p = 0.001$) with the study group. Similar results were observed by Anastasio et al.[9] in the studies with creatinine clearance and inulin clearance.

In our study, we have shown that children with hydronephrosis had decreased RFR as compared with those of healthy children and this is statistically significant ($P = 0.03$). This may be because hydronephrotic children were already in a state of persistent glomerular hyperfiltration and had limited renal reserve to increase the GFR further.

Pascual et al.,[2] reported that glomerular hyperfiltration developed as a primary phenomenon in PUJ obstruction (hydronephrosis). The trends of renal reserve in children with hydronephrosis have been shown in [Figures 1 and 2]. There is no difference in the trends of renal reserve in unilateral and bilateral hydronephrosis, although the reduction in the renal reserve was not consistent [Figure 3].

A major limitation of this study is that it does not determine whether the change in global GFR occurring in the study group following stimulation is attributed to the hyperfiltrative response of the hydronephrotic kidney or of the contralateral normal kidney in unilateral hydronephrosis. Nevertheless, the observation that in hydronephrosis the RFR is significantly reduced compared to the control group is a significant finding. Moreover, it might serve as a platform for a further study of the post-stimulation differential GFR in a larger group of subjects in a planned way. At present, it is not possible to use RFR in identifying which hydronephrotic kidney is at risk of progressive renal damage and for initiating therapeutic intervention. However, it provides an additional way to study the GFR.

It was hoped that the measurement of RFR could be used clinically to unmask the presence of severity of hydronephrosis and in combination with the knowledge of baseline GFR may give information regarding the prognosis of these patients. Unfortunately, renal reserve has not been found to be consistently reduced and is sometimes actually increased as shown in [Figure 3]. Furthermore, other factors such as the long-term level of dietary protein and possibly sodium intake may alter the RFR in any given individual. Adding to this the very wide range of RFR in both the healthy group and in children with renal disease, limits the use of RFR in the clinical field.

**CONCLUSION**

The present study reveals that RFR is preserved in children with hydronephrosis, but it is reduced in comparison to healthy children. However, because of the limitation mentioned above, its utility in clinical practice cannot be defined. There is need for a larger study to define the differential RFR and thus the renal reserve of the hydronephrotic kidney.

**REFERENCES**


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