EDITORIAL COMMENTARY

The predictive value of the renogram

Amy Piepsz

The renogram has existed for more than half a century. It was introduced as a diagnostic tool for the detection of renal obstruction. A decreased split function and/or a prolonged renal transit were the criteria used for that purpose and oriented the clinician in the direction of a surgical correction.

Unfortunately, the concept of obstruction appeared progressively to be difficult to define, except when dealing with total obstruction. This last condition can be seen for instance after accidental ligature of a ureter or in experimental models. In these cases, because there is no outflow, the inflow will disappear within 15 days after ligation and the kidney becomes nonfunctional [1]. Similarly, secondary obstruction due to stones, cancer or retroperitoneal fibrosis in adult patients can easily be demonstrated on the renogram on the basis of a continuous ascending curve, even without administration of furosemide. In some cases, a presumptive diagnosis of partial obstruction can reasonably be proposed. As a matter of fact, before the introduction of ultrasonography, congenital abnormalities such as pelviureteric junction (PUJ) stenosis or obstructive megaureter were generally detected late on the basis of severe urinary tract infection, sepsis or recurrent renal colic. The association of these symptoms with transit impairment was sufficient for the surgeon to establish a causal link and to operate upon the patient.

Things became more complicated once the hydronephrosis could systematically be detected by antenatal ultrasonography, the PUJ stenosis being confirmed postnatally within the first weeks of life. These infants are in good health and completely asymptomatic and the need for surgery was seriously questioned. Which hydronephrotic kidney was indeed obstructed and on what criteria?

Some clinicians focused on single kidney function, on the basis that a low split function (arbitrarily chosen as being below 40%) was reflecting an ongoing obstruction [2]. Strong arguments were, however, missing as a low function could be simply due to an associated dysplasia. Other clinicians considered the impairment of transit, particularly after furosemide administration, as characteristic of obstruction [3], and cooperated to define typical transit patterns. Meanwhile, the concept of "reservoir function" emerged, which explained how, even under furosemide treatment, the dilution of the tracer in an enlarged collecting system could give rise to a very abnormal transit pattern [4, 5], despite the obvious absence of obstruction. A consensus emerged on excluding obstruction in those with good renal drainage and on the impossibility of making a diagnosis in those with poor drainage [6]. The unique widely accepted definition of obstruction therefore remained a frustrating retrospective diagnosis, based on deterioration of the split function and/or a significant increase in the diameters of the collecting system on ultrasonography [7].

These constant efforts to define obstruction were paralleled by similar efforts to improve the quantitative information provided by the renogram. Tracers with high extraction rate such as ^{99m}Tc MAG3 or ^{99m}Tc EC were introduced, different approaches were combined for estimation of the input function, early furosemide injection became more popular, and the need for late images after the effect of gravity and micturition was frequently underlined,

A. Piepsz (✉)
Department of Radioisotopes, University Hospital St Pierre,
322, Rue Haute,
1000 Brussels, Belgium
e-mail: amypiepsz@yahoo.com

providing a much higher rate of good, or at least partial, renal drainage. The positive consequence of these technical advances is that renal drainage evaluation remains important, allowing a favourable evolution with a conservative approach to be predicted in the majority of those with hydronephrosis.

Besides the importance of the renogram in excluding obstruction, its main role has probably been to estimate, in the neonatal period as well as during conservative or postoperative follow-up, the functional status of the hydro-nephrotic kidney. The consequences of this quantitative approach have been that, in the majority of cases, a normal maturation of the function of the hydronephrotic kidney can be observed even with a nonsurgical approach, and the number of surgical interventions, compared to the systematic strategy before the 1960s, has decreased dramatically over the years [8].

However, attitudes towards surgery still remain extremely heterogeneous, varying from a systematic surgical approach in the early months of life [9, 10] up to a similar systematic conservative follow-up [11]. An absence of well-controlled prospective studies in this field is at least partly responsible for this situation.

In order to provide a more scientific basis to the clinical approach, experimental studies using animal models have been performed. The results were, however, essentially dependent on the type of model chosen. Chevalier et al., using a model of total or subtotal obstruction, have shown that the kidney suffering from the created obstruction developed a mechanism of functional compensation which, in the end, seemed to be harmful to the kidney [10]. Other studies, based on a model of partial obstruction, have concluded that in the long run the function of the obstructed kidney remains stable [12]. The weakness of both models is reflected in the hazardous extrapolation of the results to the particular situation of antenatally detected PUJ stenosis in children.

From a strictly semantic point of view, the definition of obstruction might in 2009 be an obsolete question. As a matter of fact, I would personally be tempted to consider all PUJ stenoses as partially obstructed kidneys since, by definition, this entity is characterized by a narrow pelviureteric segment. What matters at the end is to try to predict which kidney is at risk of deterioration if no surgery is undertaken and which kidney has a high chance of function improvement as a consequence of surgery.

Unfortunately, we have to accept that until now the renogram has been unable to serve as a predictor of renal function in the long term, except in the presence of good renal drainage. Neither poor drainage nor decreased renal function can nowadays be considered as absolute risk factors. In most clinical studies, function improvement, in the presence of low split function at entry, has been observed after surgery in only a limited number of patients. Moreover, no single controlled study is available showing that the kidney with poor function is more at risk of deterioration than the kidney with normal split function [8, 13]. Similarly, it has been shown that poor renal drainage does not necessarily represent per se a risk of renal deterioration [5, 11].

In the present issue, Schlotmann et al. [14] used a different approach. They carefully avoided choosing as a gold standard any kind of vague definition of obstruction, based for instance on the size of the enlarged cavities or the peroperative findings. Their option was to use a surrogate gold standard, namely the long-term renal function. On that basis, they provide some impressive data suggesting that the determination of parenchymal transit might show strong predictive value in estimating the functional evolution.

The principle of measurement of parenchymal transit instead of whole-kidney transit is not new and is based on the fact that cortical transit reflects the degree of renal damage due to obstruction and is not influenced by the reservoir function of the dilated collecting system. Britton et al. have undoubtedly been pioneers in this matter. They fixed some rules for the quantitation of cortical transit and showed a correlation between the length of parenchymal transit and the need for surgery [15]. There are, however, two reasons why the approach by means of cortical transit has not gained wide acceptance.

The first is related to the methodology used for measuring cortical transit. Different approaches have been published over the years and an overview on this topic can be found in a recent world consensus on renal transit [16]. In brief, one can draw a region of interest around what one thinks represents the cortical area and calculate for this area any transit parameter one wishes [15]. Another approach is to provide a parametric image of the entire kidney, one of the above-mentioned parameters being determined pixel by pixel. This approach has the advantage that it does not make any a priori statement about the limits of the cortical area. Each pixel of the image appears in a given colour representing the transit time in that pixel [17]. An even more sophisticated approach is the use of factor analysis which, in theory, is able to separate within a given renal image, different kinetics included in the same voxel. A pure cortical factor could therefore be isolated from the factor corresponding to the collecting system [18]. Unfortunately, all these approaches perform well in normal or almost normal kidneys, in which a peripheral area with normal transit can easily be demonstrated. In those with huge hydronephrosis, particularly young children, there is often an overlap between the cortical area and the renal cavities and one is unable, whatever the method used, to decide whether one is dealing with a very prolonged cortical transit

or with an overlap [19]. Another flaw which concerns all the methods mentioned is that any slight movement during acquisition might give rise to an erroneous "normal transit area".

The second weakness related to cortical transit is the absence of an adequate gold standard. Validation of cortical transit as an index of obstruction has often been based on surgical findings; this is no longer accepted. As mentioned above, the definition of obstruction is a retrospective one, based on a deterioration of split function during conservative follow-up.

It is therefore to the credit of Schlotmann et al. [14] to have elaborated an interesting design based on cortical transit and aimed at predicting the indication for surgery. Their initial hypothesis was twofold:

1. Is cortical transit able to predict a postoperative improvement of renal function in those with unilateral hydronephrosis associated with an initial low split function?
2. Can cortical transit detect those hydronephrotic kidneys in danger of deterioration, therefore indicating that a conservative approach is not appropriate?

The first question is of major importance. As a matter of fact, a review of the literature has shown that in the majority of patients, surgery does not lead to an improvement of split function, whatever the preoperative level of split function [13]. If the hypothesis of the authors is verified, cortical transit would allow the selection of the rare patients in whom such an improvement would be highly probable.

The second question is important as well. Josephson, in a wide analysis of a series of cases followed conservatively, has shown that deterioration occurs in only 10% of kidneys [8]. Undoubtedly, being able to predict in advance which kidneys are in danger of deterioration, rather than waiting for such a deterioration to occur, would allow a more adequate planning of surgery in this restricted number of cases.

The results obtained by Schlotmann et al. [14] are encouraging. According to their criteria of impaired cortical transit, eight out of ten kidneys with impaired cortical transit and low split function had a striking improvement in split function after surgery. This finding, if confirmed, would represent in itself a great advance in the strategy for deciding upon pyeloplasty. Less convincing are the results seeking to show that an impaired cortical transit time represents a risk of renal deterioration if no surgery is undertaken. Only three such cases are included in the study, two showing indeed a deterioration of function while the function remained stable in one. The lack of cases in this series is, according to the authors, explained by the fact that the surgeons are of the opinion that kidneys with prolonged cortical transit should be operated upon. The only objective data provided by Schlotmann et al. [20] and supporting that view is an experimental study on total or subtotal obstruction which is unlikely to reflect the partial obstruction existing in PUJ stenosis [21].

Finally, one has to question the methodology used by the authors to define what is impaired cortical transit. As mentioned above, the limitations and pitfalls related to the determination of cortical transit are not negligible, even when sophisticated quantitative methods of measurement are used. In the present paper, the authors have chosen a nonquantitative approach, the scientific value of which relies mainly on a rather good interobserver reproducibility (about 15% disagreements). Several criteria have been used, the most important of which seems to be a very late appearance of tracer within the pelvis, with a pure cortical image persisting for 8 minutes. This suggests that only extremely prolonged cortical transit times associated with nonfilling of the collecting system were selected, explaining that the disturbing superimposition between true cortical tissue and cavities is likely to have been avoided in these cases. It is also possible that the different criteria used by the authors to define prolonged cortical transit might also include a poor response to furosemide and a low split function. As a matter of fact, having almost no activity appearing in the pelvis implies that no response to furosemide can be expected, and this was indeed what was observed in all cases. Similarly, the criterion of a progressive increase in parenchymal activity probably reflects the decreased function of that kidney and not necessarily impaired cortical transit. A low split function was indeed observed in all cases with impaired cortical transit. The authors have shown that both the response to furosemide and the low function were per se not valuable predictive criteria. It is, however, not excluded that the combined use of quantitative parameters of poor drainage [22, 23] and low unilateral function might perform as well as cortical transit.

Nevertheless, the work of Schlotmann et al. is a step forward in a good direction, and it is hoped that further pilot studies using similar designs will be undertaken and will confirm the two initial statements of the authors. It is time for renography to become a tool for predicting those kidneys which might really benefit from a surgical procedure.

References

1. Schelfhout W, Simons M, Oosterlinck W, De Sy WA. Evaluation of 99mTc-DMSA renal uptake as an index of individual kidney function after acute ureteral obstruction and desobstruction. An experimental study in rats. Eur Urol 1983;9:221–6.

2. Gordon I, Dhillon HK, Gatanash H, Peters AM. Antenatal diagnosis of pelvic hydronephrosis: assessment of renal function and drainage as a guide to management. J Nucl Med 1991; 32:1649–54.

3. Conway JJ, Maizels M. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council–The Society of Nuclear Medicine. J Nucl Med 1992;33:2047–51.

4. Piepsz A, Ham HR, Erbsmann F, Hall M, Diffey BL, Goggin MJ, et al. A co-operative study on the clinical value of dynamic renal scanning with deconvolution analysis. Br J Radiol 1982;55:419–33.

5. Amarante J, Anderson PJ, Gordon I. Impaired drainage on diuretic renography using half-time or pelvic excretion efficiency is not a sign of obstruction in children with a prenatal diagnosis of unilateral renal pelvic dilatation. J Urol 2003;169:1828–31. doi: 10.1097/01.ju.0000062640.46274.21.

6. Gordon I, Colarinha P, Fettich J, Fischer S, Frökier J, Hahn K, et al. Guidelines for standard and diuretic renography in children. Eur J Nucl Med 2001;28:BP21–30.

7. Koff SA, Campbell K. Nonoperative management of unilateral neonatal hydronephrosis. J Urol 1992;148:525–31.

8. Josephson S. Antenatally detected, unilateral dilatation of the renal pelvis: a critical review. I. Postnatal non-operative treatment 20 years on – is it safe? Scand J Urol Nephrol 2002;36:243–50.

9. King LR, Hatcher PA. Natural history of fetal and neonatal hydronephrosis. Urology 1990;35:433–8. doi:10.1016/0090-4295 (90)80087-4.

10. Chevalier RL, Chung KH, Smith CD. Renal apoptosis and clustering following ureteral obstruction: the role of maturation. J Urol 1996;156:1474–9. doi:10.1016/S0022-5347(01)65633-7.

11. Ulman I, Jayanthi VR, Koff SA. The long-term follow up of newborns with severe unilateral hydronephrosis initially treated nonoperatively. J Urol 2000;164:1101–5. doi:10.1016/S0022-5347(05)67262-X.

12. Piepsz A, Ham HR, Hall M, Thoua Y, Froideville JL, Kinthaert J, et al. Long-term follow-up of separate glomerular filtration rate in partially obstructed kidneys. Experimental study. Scand J Urol Nephrol 1988;22:327–33.

13. Eskild-Jensen A, Gordon I, Piepsz A, Frøkiaer J. Congenital unilateral hydronephrosis: a review of the impact of diuretic renography on clinical treatment. J Urol 2005;173:1471–56.

14. Schlotmann A, Clorius J, Clorius SN. Diuretic renography in hydronephrosis: renal tissue tracer transit predicts functional course and thereby need for surgery. Eur J Nucl Med Mol Imaging. doi:10.1007/s00259-009-1138-5.

15. Britton KE, Nimmon CC, Whitfield HN, Hendry WF, Wickham JE. Obstructive nephropathy: successful evaluation with radionuclides. Lancet 1979;1:905–7. doi:10.1016/S0140-6736(79)91377-1.

16. Durand E, Blaufox MD, Britton KE, Carlsen O, Cosgriff P, Fine E, et al. International Scientific Committee of Radionuclides in Nephrourology (ISCORN). Consensus on renal transit time measurements. Semin Nucl Med 2008;38:82–102. doi:10.1053/j.semnuclmed.2007.09.009.

17. Dobbeleir AA, Piepsz A, Ham HR. Pixel-by-pixel mean transit time without deconvolution. Nucl Med Commun 2008;29:345–8. doi:10.1097/MNM.0b013e3282f4d318.

18. Sámal M, Nimmon CC, Britton KE, Bergmann H. Relative renal uptake and transit time measurements using functional factor images and fuzzy regions of interest. Eur J Nucl Med Mol Imaging 1998;25:48–54.

19. Piepsz A, Ham HR, Dobbeleir A, Hall M, Collier F. How to exclude renal obstruction in children? Comparison of intrarenal transit times, cortical times and the frusemide test. In: Joekes AM, Constable AR, Brown NJG, Tauxe WN, editors. Radionuclides in Nephrology. London: Grune and Stratton; 1981. p. 199–204.

20. Schlotmann A, Clorius JH, Rohrschneider WK, Clorius SN, Amelung F, Becker K. Diuretic renography in hydronephrosis: delayed tissue tracer transit accompanies both functional decline and tissue reorganization. J Nucl Med 2008;49:1196–203. doi:10.2967/jnumed.107.049890.

21. Piepsz A. Can delayed cortical transit identify those kidneys whose function is at risk? J Nucl Med 2009;50:168–9. doi:10.2967/jnumed.108.056630.

22. Chaiwatanarat T, Padhy AK, Bomanji JB. Validation of renal output efficiency as an objective quantitative parameter in the evaluation of upper urinary tract obstruction. J Nucl Med 1993;34:845–8.

23. Piepsz A, Tondeur M, Ham H. NORA: a simple and reliable parameter for estimating renal output with or without frusemide challenge. Nucl Med Commun 2000;21:317–23. doi:10.1097/00006231-200004000-00005.