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International Scientific Committee of Radionuclides in Nephrourology (ISCORN) Consensus on Renal Transit Time Measurements

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This report is the conclusion of the international consensus committee on renal transit time (subcommittee of the International Scientific Committee of Radionuclides in Nephrourology) and provides recommendations on measurement, normal values, and analysis of clinical utility. Transit time is the time that a tracer remains within the kidney or within a part of the kidney (eg, parenchymal transit time). It can be obtained from a dynamic renogram and a vascular input acquired in standardized conditions by a deconvolution process. Alternatively to transit time measurement, simpler indices were proposed, such as time of maximum, normalized residual activity or renal output efficiency. Transit time has been mainly used in urinary obstruction, renal artery stenosis, or renovascular hypertension and renal transplant. Despite a large amount of published data on obstruction, only the value of normal transit is established. The value of delayed transit remains controversial, probably due to lack of a gold standard for obstruction. Transit time measurements are useful to diagnose renovascular hypertension, as are some of the simpler indices. The committee recommends further collaborative trials.
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This Consensus Conference document addresses a class of techniques, namely the methods to assess renal transit time (TT) with radionuclides (including simplified methods providing transit indices) and the usefulness of this information for patients. The objectives of this consensus were:

- to describe the advantages and the drawbacks of the different techniques for measuring or assessing renal transit;
- to review the validation studies (methodological, experimental, and clinical) that have been undertaken to justify a given technique;
- to propose to the reader one or several valuable approaches in clinical routine; and
- to define the types of studies still missing and to suggest their possible designs.

Methodology

A first draft was discussed by the committee by e-mail. Then, an outline was proposed by Dr. Durand and approved by the

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Note: Throughout the text, the symbol "±" stands for standard deviation.

Conflicts of interest: K.E.B. was a consultant to Nuclear Diagnostics Ltd (Hermes work stations) from October 2004 to October 2005; he is no longer involved with this company.

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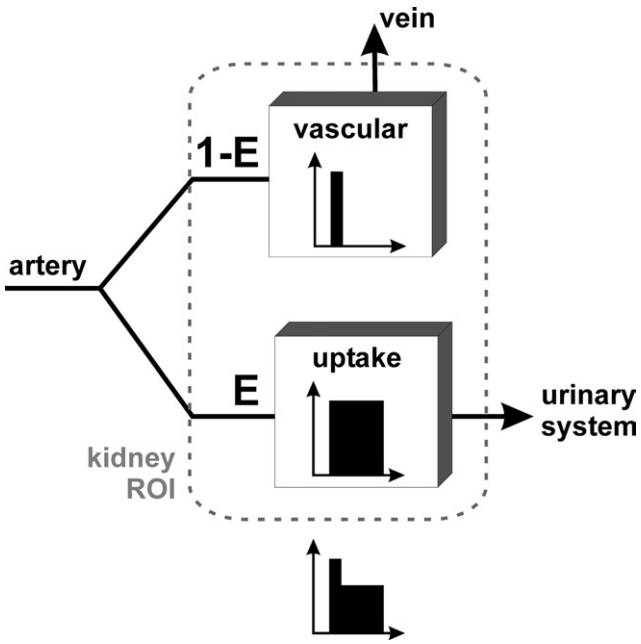

Figure 1 Probability for a single molecule to stay in the renal ROI.

other committee members. The whole text was then rewritten based on this outline by Dr. Durand and Dr. Blaufox, including the comments and new references that were proposed and classifying the level of evidence of the references. This version was then submitted to the committee for comments and changes. It is reminded here that a consensus does not mean that all the authors agree with every word that is printed.

Basic Facts on Renal TT

In 1956, Taplin and coworkers published the use of ^{131}I-diodrast injected intravenously to produce dynamic acquisitions of kidneys, thus obtaining a time-activity curve.[1] These time-activity curves can be used to derive relative renal function,[2] but they also provide information on transit, that is, time during which the tracer stays in a given part of kidney. A quantitative analysis of the renogram suggesting the use of deconvolution was proposed as early as 1964.[3] Very early, it was suggested that studying renal transit time could be useful.[4-8] In 1975, Kenny and coworkers described the measurement of transit times in a series of 300 patients with various renal diseases and suggested that transit was mostly lengthened in obstruction.[9]

Transit Time

TT can be defined as the time that the tracer would stay in a given region if it were injected as a bolus directly into the renal artery and if no tracer recirculation occurred.[10] This time reflects the behavior of a single molecule.[11] If E refers to extraction, then a molecule entering the kidney has a probability of E to be taken up by the kidney then staying in the region of interest (ROI) until it leaves by the urinary tract, and a probability of $(1 - E)$ to stay only a short time in the vascular bed, then leaving the ROI by the vein (Fig. 1). For example, for diethylene-triamine-penta-acetic-acid (DTPA), a molecule has an 80% probability of staying in the vascular bed, with a transit of a few seconds, and a 20% probability of being filtered, then staying at least a few minutes in the tubules before leaving the kidney by the ureter.[12] This results in a function, called the renal retention function (RRF). This function, also known as impulse response function, or residue function will be noted $R(t)$. It gives the probability that a molecule that entered the kidney at time 0 is still remaining in it at time t. In fact, as the pathways inside kidneys are not of the same "lengths," there is a distribution of transit times, which results in a more complex shape for R (Fig. 2).

Various TTs

When analyzing the shape of R, it is possible to define several characteristic times (Fig. 3). Also, although it is out of the scope of this consensus, it is noteworthy that the plateau height R_k (Fig. 3) is proportional to individual renal function.[13] A transit time is the time that a given molecule remains

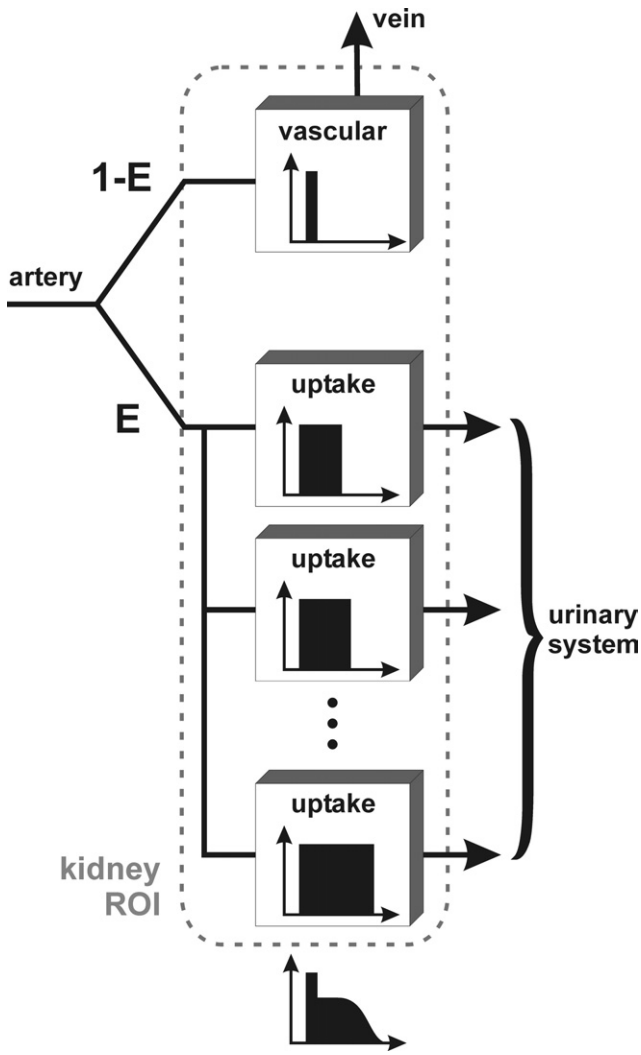

Figure 2 Distribution of transit times.

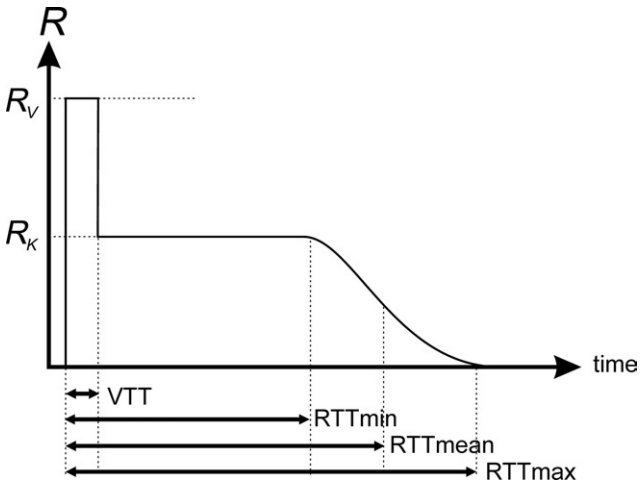

Figure 3 Shape of the renal retention function. Here, for simplicity sake, the vascular transit time (VTT) is assumed unique. The renal transit time (RTT) is distributed between a minimal (RTTmin) and a maximal (RTTmax) value with an average of RTTmean.

in a given domain. Several variants of renal transit time (RTT) can be defined (Fig. 3) according to the region considered:

- Vascular transit time (VTT): time span when a molecule of tracer stays in the renal vascular bed after entering kidney and before getting out[14];
- Whole kidney transit time (WKTT): time span when a molecule stays in the whole renal ROI; this time encompasses sojourn in vascular bed, nephrons and pelvicalyceal system;
- Parenchymal transit time (PTT): this is the time span between entering the nephron via renal artery and entering the calyces/pelvis; and
- Pelvic transit time (usually defined as WKTT – PTT).

It should be noted that assessing the transit in renal parenchyma or in pelvicalyceal cavities probably have very different physiological significance. Moreover, as already seen, because renal structures are not uniform, the transit time is not unique but follows a distribution that can be characterized by several parameters:

- its average value: mean transit time (MTT);
- its minimal value (minRTT);
- its maximal value (maxRTT);
- the parenchymal transit time index, defined as the difference between mean and minimal transit times: PTTI = MPTT – minPTT, has been suggested to diagnose obstructive nephropathy[15-17];
- the standard deviation of transit times SDTT was proposed and claimed similar to the PTTI but easier to calculate and more robust[18]; and
- The time to decrease the RRF to 20% of its maximal value (T20).[19]

It was also proposed to deconvolve the pelvis activity by the cortical activity to provide a pelvic retention function,[20] which aimed to characterize the urinary upper tract regardless of its input. This index was not further studied. It must be emphasized that the term TT has been used in some publications where it has been defined as the time delay between the appearance of the tracer in two distinct regions.[21] This usage is indeed a simple qualitative index of renal transit, but it is not generally accepted as a reproducible and quantifiable measure of transit time.

Convolution

Direct measurement of this time is obviously impossible in routine where tracer enters the kidney continuously, given by the plasma time activity curve $P(t)$. However, everything happens as if the kidney were receiving an infinite number of infinitely small intraarterial injections, shifted in time and scaled by $P(t)$. The effect of each of these injections is given by the RRF, also shifted in time and scaled by $P(t)$. Summation of all the effects of the small injections results in the renogram $K(t)$. This is illustrated in Fig. 4. Mathematically, this operation is called a convolution product[22] and it is written as follows:

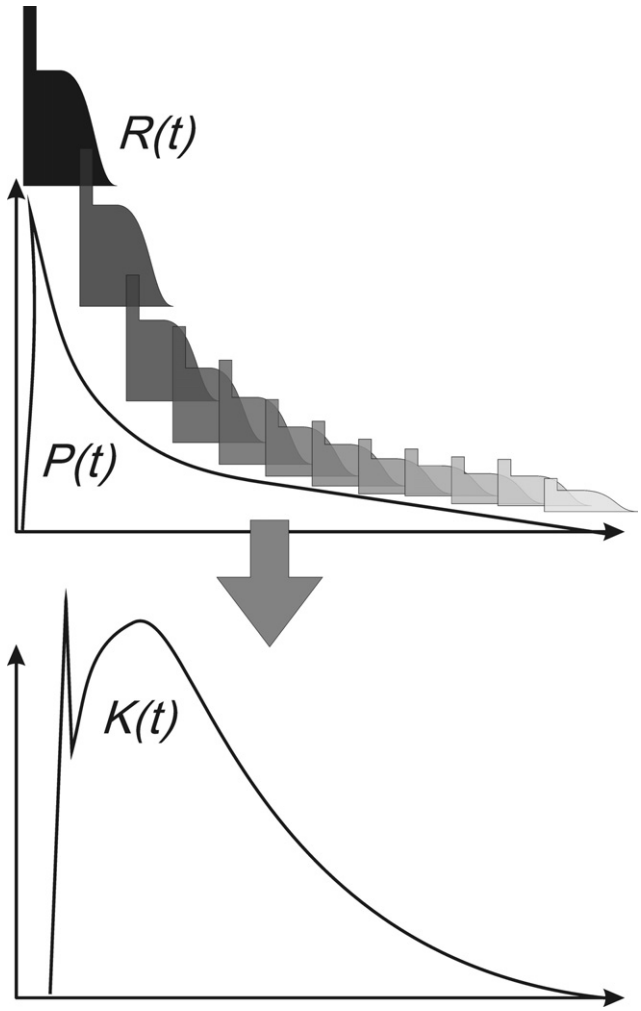

Figure 4 If $R(t)$ is the renal retention function and $P(t)$ is the plasma-time activity curve, the renogram $K(t)$ can be seen as the result of sum of many small injections shifted in time and scaled by $P(t)$, each of these injection having the behavior of $R(t)$.

$$K(t) = (P * R)(t) = \int P(\tau) \times R(t - \tau)\, d\tau \qquad (1)$$

(Note: This formulation is explained more accurately and thoroughly in the appendix published online at http://www.ISCORN.org.)

The renogram is therefore the convolution product of the plasma-time activity curve P and of R. In fact, R is the idealised renogram that would have been observed if a small intraarterial bolus (approximating what mathematicians describe as a Dirac distribution and noted δ) had been injected, without any recirculation (Fig. 5).

Both K and P can reasonably be measured routinely, so to infer R, one only needs to invert Eq. 1. This is called deconvolution and can be done in various ways. Therefore, in theory, it is possible to indirectly determine $R(t)$ and hence measure transit times in the kidney. This deconvolution approach was validated against direct injection into renal artery in man.[23] In this study, routine renal arteriography was used to perform renography by injecting DTPA directly into the renal artery with correction for tracer recirculation. The RRF obtained from this direct approach was compared with deconvolution obtained from classical renography and they matched reasonably well, with good agreement for MTT.

The approach of convolution is valid under two general assumptions:

- linearity (which should in practice be fulfilled if we neglect attenuation and scattering)[24] and
- stationarity, that is, time invariance (which is discussed in the section "Renal Transit Measurement by Deconvolution Techniques")

Pathophysiological Meaning of TT

Despite an abundant literature on transit times, not many data have been published about its pathophysiological meaning. Direct consequences of a long transit time can be driven in two circumstances: when urine stagnation facilitates bacterial infection or crystal growth in urolithiasis.[25] Except for these conditions, the transit time should be considered as a complex parameter which depends on both flow Q and volume V. In a simple pipe model, whatever the velocity distribution, the mean transit time is related to flow and volume by the following equation[26]:

$$\mathrm{MTT} = V/Q$$

Interestingly, the same relation arises in a simple reservoir model with a single compartment, when diffusion and convection dominate flow. Transit time can therefore be increased by volume increasing or by flow decreasing.

For VTT

For VTT, the considered volume is the renal blood volume and increase in VTT would be related to high resistance leading to reduced flow.[27]

For PTT

For PTT, the considered volume is the nephron volume for DTPA (which is filtered) and effective tubular volume for mercaptoacetyl-tri-glycine acid (MAG3) (which is mostly secreted). (Note: The behavior of MAG3 within the nephron cells must also be considered.) The primary urine flow is the glomerular filtration rate (GFR) and thus directly corresponds to renal function. Transit is therefore strongly linked to renal function.[28] The final urine flow depends mostly on hydration state. Of course, along the tubule, water and solute reabsorption occurs so flow decreases continuously. Diuretics and downstream resistance may also influence flow. The dependence of mean parenchymal transit time (MPTT or $\mathrm{PTT}_{\mathrm{mean}}$) on urine flow was shown in animal models.[29] A decrease in renal perfusion pressure leads to greater water reabsorption, smaller urine flow and increased MPTT.[30] This effect occurs in approximately 6 seconds.[31]

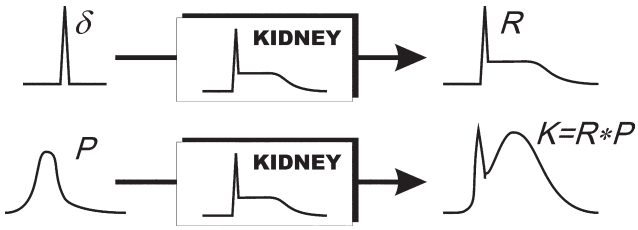

Figure 5 Convolution product: when a small unit intraarterial injection δ (Dirac) enters the kidney, this results in the renal retention function (RRF) $R(t)$; when the input is different (here P), the result is the convolution product of P and R, which gives the renogram.

For Whole Kidney TT

For whole kidney transit, the effect on parenchyma is mixed up with the effect on pelvicalyceal system. In hydronephrosis, pelvicalyceal cavities are, by definition, enlarged, which increases MTT. It has been shown that pelvic size is correlated with washout rate.[32] These authors even suggested that enlarged pelvic size was mostly responsible for washout delay. Assessing pelvic volume may help to understand the variations of RTT in hydronephrosis.[33] Mean transit time for whole kidney (MWKTT) was also negatively correlated with urine flow rate but the relationship was less clear than for MPTT possibly because of variations of the cavity volume.[29] Other authors found MPTT less dependent on hydration state than MWKTT because tubular urine is less concentrated than pelvic urine.[34,35] However, in humans, the hydration state has been shown to influence MWKTT only slightly[19] so it is still not clear whether the hydration state influences MPTT or MWKTT more.

Alternate Techniques to Measure TT

Electron-beam tomography (EBCT) was used to assess transit in animal models (Fig. 6).[36,37] Dogs do not have papillae, so when using a scanner slice, images can be obtained without any superimposition of structures. The problem is different for a dynamic projection of the renal scan in humans where distinction between different portions of nephrons cannot be made. Some recent attempts were tried to assess transit with MRI but the methodology is not well defined yet.[21,38]

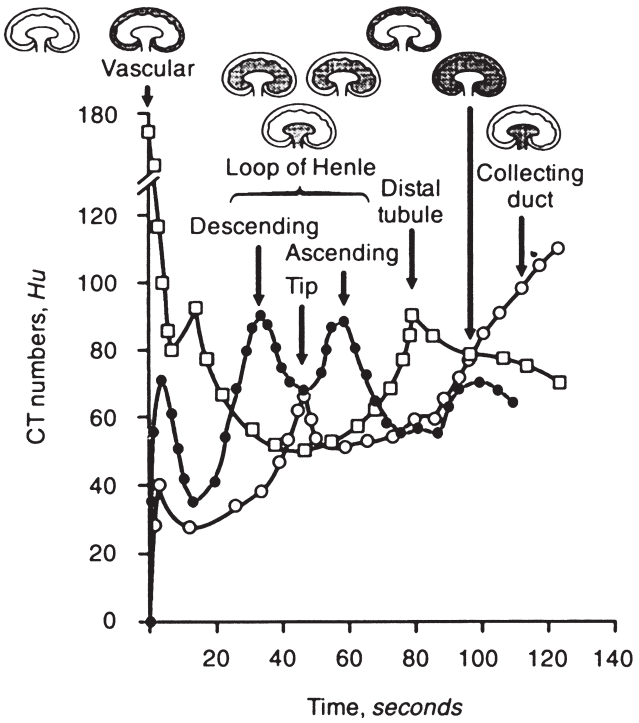

Figure 6 Transit times measured by EBCT (time-activity curves are shown). (Reprinted with permission from Macmillan Publishers, Ltd: *Kidney International*, 1996.[37])

Assessment of Transit

The general technique to assess renal transit in nuclear medicine is to acquire a dynamic scan after a bolus injection. After acquisition, either a qualitative assessment of transit can be done or a quantitative one, which may be either a transit time determination or assessment of a simpler index of transit. (Here, "simple" indices should be understood as "easy to determine." They may however reflect less simple physiologic parameters.)

Acquisition Parameters

The recommendations proposed here are focused on transit. However, renography should not be optimized to yield an accurate result of only one parameter. It should be designed to yield acceptable results for several aspects of the examination, such as split renal function, perfusion, morphology and transit. The reader may find the reference data in previous consensus or published guidelines.[2,39-43]

Patient

Dehydration may induce functional renal impairment and slow transit (see "Synthesis") so patient should at least be normally hydrated (diuresis renography is mentioned in the section "Diuresis Renography"). Oral hydration is sufficient. The patient should be either lying supine or sitting or in a reclining position (supine is preferable to avoid motion but further acquisition after upright posture is usually mandatory: see "Gravity-Assisted Drainage [Upright Posture]). The patient should be instructed to remain still during the procedure or motion should be restrained.

Radiopharmaceutical

The transit of glomerular agents such as inulin or ^{99m}Tc-DTPA is straightforward: after entering the renal artery, they are rapidly filtered and progress along the nephron until its end. Intrarenal transit of purely secreted substances is not so well-known because of the time needed in the tubule from basal uptake until apical secretion into the lumen. Finally, tracers such as hippuran (orthoiodohippurate-OIH) or ^{99m}Tc-MAG3 are both filtered and secreted so their transit depends on more parameters and reflects something more complicated. However, because of the higher extraction, tubular tracers have been more widely used for assessing urinary transit[39] and for diuresis renography.[44] In theory, the initial pathways are different between the two tracers, MAG3 being secreted in the proximal tubule whereas DTPA is filtered. However, at the end of the proximal tubule, they share the same behavior and, in practice, transit times were found similar with MAG3 and DTPA. Both tracers are therefore acceptable, with a preference for MAG3 because of greater extraction.

The usual injected activities in adults are 150 MBq for MAG3 or 300 MBq for DTPA.[39,45] For children, the injected activities should follow the EANM recommendations.[46] At the present time, ^{123}I-hippuran is not used much because it is expensive (recommended activity for adults was 20 MBq). Transit of L, L-ethylenedicysteine (L,L-EC) was also tested against MAG3 without significant difference.[47] Simulations suggest that, even if noise leads to underestimating MTT, high injected activities are not mandatory, at least for MTT.[48] Similarly, simple indices do not require high activities. On the contrary, a British standardization group recommended that whole kidney reach at least 1,000 cps at peak.[49] No consensus could be reached on injected activity: some members advocated injecting higher activities to improve statistics (especially for PTTI) but the majority agreed to keep with these values.

Camera

The gamma-camera should be fitted with an all-purpose, low-energy collimator, with kidneys and heart in the field of view. Including bladder makes it possible to assess its fullness. The acquisition should be performed as a posterior view, except for transplants.

Dynamic Sequence

The sequence should start just before the tracer injection. Sequence duration is a matter of debate. If a diuresis renography is performed with a F + 20 protocol, a long acquisition (40 minutes) is preferable. In other circumstances, 20 minutes is usually recommended, except when very long transit times are expected. Indeed, to properly measure transit, the study should last longer than the maximum TT. If not, the whole retention function will not be completely determined, which will induce a bias.[50] Therefore, when the RRF does not fall to zero at the end of the study, it should be mentioned that the transit time is longer (>) than the calculated value. For vascular transit time, which is short (a few seconds), a high rate (1 image per second) is recommended, with the

drawback of poor counting statistics. Whenever a cardiac curve is used (deconvolution, output efficiency or Patlak-Rutland plotting), 10 s images are recommended.[39,40] In other cases, 10- to 20-second images are acceptable. For VTT, 1-second images should be used. Although usually provided, matrix size is not the most relevant parameter: pixel size is. However, with large-field cameras, a 128 × 128 matrix is usually recommended[39] to get a pixel size of about 3 to 5 mm. Zoom is recommended for small children. It should be set so that the image should contain only the area between the lower part of the heart and the bladder.

Obtaining of the Renogram

Renal ROI

The renal ROI can either encompass the whole kidney, including pelvis, or select parenchyma. For functional assessment, a whole kidney is necessary. Parenchymal ROIs may be drawn by hand with the help of a parametric image such as a transit time image,[16,51,52] T_{max} image, NORA image, or OE image (q.v.).[53] Also, two images (early for parenchyma and late for cavities) may be superimposed to help drawing.[54] Alternatively, the renogram can be derived from factorial analysis, which is sometimes called "fuzzy ROI."[55] However, there is no reason why mathematical components extracted this way would correspond to physiological components[53] unless a priori information is added to the model. It must be noted however that in nuclear medicine, because of unavoidable breathing motion, the kidney image is somewhat blurred. This motion, obvious when looking at dynamic MRI images, is not visible as such in nuclear medicine because of the poor temporal and spatial resolutions that are used. The effect exists however and can induce difficulties in differentiating cortex from pelvicalyceal system.

Background Subtraction for Kidney

A kidney ROI contains at the same time vascular activity, parenchymal (extracted) activity, and nonrenal activity. As shown in the first section, parenchymal activity is of interest and vascular activity is dealt with by the deconvolution techniques. However, nonrenal activity remains and should be subtracted lest underestimation of MTT would occur.[48] The influence of non renal background on MTT is discussed: some authors have found it around 6%[24] or even negligible.[56] Probably, as for assessment of renal function, background subtraction is of more importance if renal function is low. As the procedure is very simple and because some published works support this, we recommend background subtraction. Perirenal ROI was the recommendation of the international consensus on renal function.[2] However, it cannot be recommended for transit calculations because it will contain pelviureteral activity. So renal background ROIs should exclude the ureteral activity from the background ROI.[40]

Zero Time

For TT measurement, a duration is measured so the choice of the origin of time has no effect. However, other simplified indices are related to time. The recommended time for this is the maximum in the input function obtained from the ROI positioned over the heart (left ventricle).

Patient Motion Correction

Motion should be checked for after the procedure. Motion violates stationarity and compromises the calculation of TT. Moreover, a kidney moving out of the renal ROI could mimic good drainage. Also, motion will affect pixel-by-pixel measurement parameters; however, small motion (or registered images after large motion) may not be a problem for global activity measurement in one large ROI. Where necessary, a movement correction algorithm should be applied to the data before application of the renal transit analysis.

Acquisition of the Input Function

Theoretically, the ideal input function would be the tracer concentration in the renal artery. However, because of small size, it is not a solution in practice and even the aorta is not recommended. The ROI of choice for the input function $C(t)$ should be the left ventricle. If the time shift between left ventricle and renal artery requires correction for perfusion analyses, this time shift is probably negligible compared with the image time (10 to 20 seconds) and therefore correction is not recommended. During this time shift, the bolus also experiences smearing. To support this point, it was shown that even after an intravenous bolus injection, since tracer travels faster in the center of the vessel, the bolus will smear about 20% of its mean transit time in an artery and twice this in lungs.[57] The effect of the latter on transit has not been assessed. In contrast, this effect may not be negligible for VTT.

The cardiac curve $C(t)$ does not reflect only the plasma concentration $P(t)$ but also interstitial background activity.[58] Indeed, unsubtracted extracardiac activity leads to underestimation of MTT[48,59] Ideally, the right proportion for subtraction can be determined by two plasma samples: if the blood pool is described by the time-evolution $P(t)$ and the heart (left ventricle) ROI by the time evolution $C(t)$, one must consider that C also contains background activity that is proportional to the activity in a background ROI $X(t)$. Then, $C(t) = a \times P(t) + c \times X(t)$, where a and c are two constants. Because $C(t)$ and $X(t)$ can be measured with gamma-camera, $P(t)$ can be sampled for two values of time so one can easily infer a and b and therefore get a true blood curve $P(t)$ instead of the heart curve $C(t)$ with a more realistic retention function.[60] However, blood-sampling is cumbersome; therefore, finally, we also recommend simple background subtraction for the input curve to get a better estimation of $P(t)$ from $C(t)$. The ROI should be placed between the upper poles of the kidneys avoiding pelviureteral activity. The suggested factor for subtraction is 0.57.

Parameters Assessing Renal Transit

To assess renal transit, two different groups of methods were developed: measurement of TT using deconvolution and estimation of renal transit through various indices. When dealing with a patient, it may be both useful to obtain a parameter with a continuous value, which makes follow up possible, and a binary response, possibly through a threshold: eg, is

surgery recommended (or not)? For quantitative parameters, only thresholding leads to a binary choice since all parameters are intrinsically continuous. One drawback of pooling many studies is that thresholds were determined retrospectively on the tested population.

Renal Transit Measurement With Deconvolution Techniques

Deconvolution techniques can be divided into two main categories: on one hand "exact" methods (matrix, Fourier, Laplace, orthogonal polynomials), where *R* is calculated from the renogram and the input function and, on the other hand, "nonexact" methods (constrained least-square) where *R* is estimated using a priori information on its shape. (Details can be found in the appendix online at http://www.ISCORN.org.) Convolution equation is valid under the assumption of linearity and stationarity. In practice, many circumstances can violate the stationarity hypothesis:

- diuretics change the output flow;
- bladder filling may cause increasing resistance to the upper urinary system;
- pelvicalyceal filling (especially after hydration and diuretics) changes the transit because of volume,[61] especially during diuresis renography;
- urinary output to the ureters and bladder is not continuous but peristaltic (this should have only a slight effect given the high frequency of peristalsis compared with the acquisition rate);
- renal plasma flow can change rapidly over time;
- a reflex pelvic contraction induced by swallowing was suggested by one study[62];
- patient motion[24];
- intermittent obstruction[63]; and
- reflux.[64]

Under the term RTT, many different parameters were assessed. Their normal values are detailed hereafter under various conditions of hydration (unless otherwise specified, these values were obtained without diuretics). When renography incorporates a TT measurement, the consensus committee recommends displaying in the report, as a quality control, the renal retention function *R* and the reconvolution curve *R***C* (ie, the convolution product of the calculated retention function with the input curve).

Vascular transit time. VTT has been only sparsely studied. Theoretically, it is independent of the radiopharmaceutical. Normal VTT depends on age, ranging from about 5 ± 1.4 seconds to about 11 ± 2 seconds in older people.[12] In normal transplants, VTT was less than 14 seconds.[27]

Parenchymal (cortical) transit time (PTT). Normal parenchymal (or cortical) mean transit time (MPTT) for DTPA is usually found between 2 and 3 minutes, depending on studies, age and hydration state (Fig. 7):

- From 2.7 ± 0.8 minutes (163 ± 49 seconds) in young (1-9 years) to 4.7 ± 1.3 minutes (280 ± 79 seconds) in elderly (70-79 years) people[12];

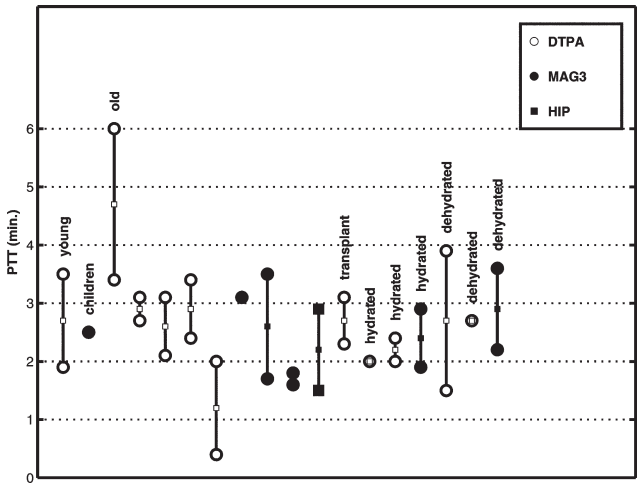

Figure 7 PTT normal values (central squares indicate mean values and lines show one standard deviation).

- 2 minutes (120 seconds) in a child, hydrated (1 L/1.73 m^2 body surface area)[34];
- 2.2 ± 0.2 minutes (131 ± 24 seconds) (hydrated)[35];
- 2.7 ± 1.2 minutes (163 ± 71 seconds) (dehydrated)[35];
- 2.7 minutes (160 seconds) (child, dehydrated)[34];
- 2.9 ± 0.2 minutes (171 ± 11 seconds)[65];
- 2.6 ± 0.5 minutes[66];
- 2.9 ± 0.5 minutes[67];
- 1.2 ± 0.8 minutes[68]; and
- 2.7 ± 0.4 minutes in transplanted kidneys.[69]

For MAG3, normal values lie in the same range:

- 1.7 to 4.5 minutes[70];
- 86 ± 0.98 (158 ± 53 seconds)[71];
- 2.4 ± 0.5 minutes (144 ± 30 seconds) (hydrated)[35];
- 2.9 ± 0.7 minutes (173 ± 41 seconds) (dehydrated)[35]; and
- 1.7 ± 0.1 minutes (104 ± 7 seconds)[72]

Hippuran yields similar results[70]:

- 2.2 ± 0.7 minutes[66]
- 2.5 minute (upper limit 7.4 minutes) in children[73]

Coefficient of variation was calculated in a model and found to be 5.2% when only Poissonian noise was considered.[24] PTT is less affected by dehydration than other parameters such as WKTT, NORA, Tmax, $T_{1/2}$.[35] One problem of parenchymal transit times in that, in practice, in a renal scan, there is not clear distinction between pure parenchyma and cavities, so determining this transit time is a technical challenge, especially for small children and when parenchyma is thinned by dilated cavities.[74]

Whole kidney transit time. Normal MWKTT for DTPA is somewhat longer than parenchymal TT (usually in the range 2-4 minutes), depending on studies, age and hydration state (Fig. 8):

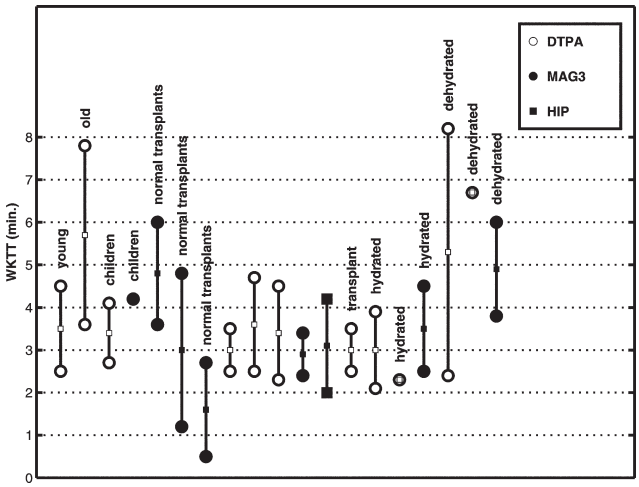

Figure 8 WKTT normal values (central squares indicate mean values and lines show one standard deviation).

- from 3.5 ± 1 minutes (209 ± 60 seconds) in young (1-9 years) to 5.7 ± 2.1 minutes (343 ± 128 seconds) in elderly (70-79 years) people[12];
- 3 ± 0.9 minutes (180 ± 55 seconds) (hydrated)[35];
- 2.3 minutes (140 seconds) (child, hydrated) (1 L/1.73 m^2)[34];
- 5.3 ± 2.9 minutes (315 ± 171 seconds) (dehydrated)[35];
- 6.7 minutes (400 seconds) (child, dehydrated)[34];
- 3 ± 0.5 minutes[20];
- 3.6 ± 1.1 minutes[19];
- 3.4 ± 1.1 minutes[66];
- 3.4 ± 0.7 minutes[19] in children; and
- 3.0 ± 0.5 minutes in transplanted kidneys.[69]

For MAG3, the normal values were much more scattered:

- 3.5 ± 1 minutes (211 ± 62 seconds) (hydrated)[35];
- 4.9 ± 1.1 minutes (291 ± 63 seconds) (dehydrated)[35];
- 2.9 ± 0.5 minutes[71];
- 4.2 minutes (upper limit 8.2 minute) in children[73];
- 4.8 ± 1.2 minutes in normal transplants[75];
- 3.0 ± 1.8 minutes in normal transplants[76]; and
- 1.6 ± 0.1 minutes (93 ± 7 seconds) in normal transplant.[72]

MWKTT for Hippuran lay in the same range:

- 3.1 ± 1.1 minutes[66] and
- 2.2 ± 0.3 minutes (134 ± 16 seconds)[9]

Coefficient of variation was calculated in a model and found to be 3.2% when only Poissonian noise was considered.[24]

Intrarenal flow and parenchymat transit time index. Several attempts were made to differentiate two populations of nephrons (namely cortical and juxtaglomerular) by their TTs. By analyzing the spectrum of transit times, Gruenwald proposed to analyze the distribution of renal blood flow between two populations of nephrons and found a reduced cortical flow in hypertensive subjects compared with normotensive.[77] Wilkinson found similar results in cirrhosis.[78] To diagnose obstructive nephropathy, Britton proposed to use the parenchymal transit time index ie, the difference between the mean PTT and the minimal PTT.[16] The rationale of this index is to detect the increased proximal tubular reabsorption of salt and water slowing transit. This assumes that the medullary concentrating ability is reduced when there is an increased resistance to outflow, subtracting minimal TT would make this index less influenced by hydration state. No consensus was reached on this index. One drawback of this approach is its lack of precision when determining the slight inflection where the curve deviates from its plateau. This is especially true when one considers that in real life, the plateau is not perfectly horizontal. Help could come however from the Patlak-Rutland plot (the deviation from linearity corresponds to the minimal transit time). Like the standard deviation of PTT (SDPTT), PTTI is therefore an index of dispersion of PTT. However, SDPTT was claimed more robust.[18]

Normal values for PTTI were mostly set for DTPA (Fig. 9):

- under 2.6 minutes (156 seconds) (with Whitaker's test as a reference)[16];
- 1.4 ± 0.4 minutes (81 ± 24 seconds)[79]; and
- 1.1 ± 0.4 minutes (67 ± 25 seconds).[80]

Similar values ware found for hippuran:

- 1.1 ± 0.3 minutes (63 ± 17 seconds).[80]

Jung and coworkers measured the SD of DTPA MPTT and found a difference between the hydrated (0.4 minute.) and dehydrated state (1.1 minutes).[35] This shows that the dispersion of cortical transit time depends on hydration state and strongly suggests that PTTI does also.

Synthesis. The term TT does not reflect a unique parameter because of the many types of TT, sometimes sharing the same name (eg, some authors refer to PTTI as PTT). In animal models, reproducibility for MTT was experimentally shown

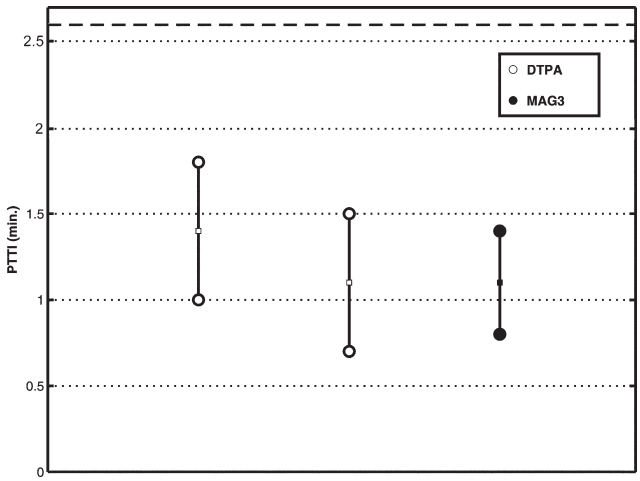

Figure 9 PTTI normal values (squares indicate mean values and lines show one standard deviation; dashed line indicates upper limit for normal).

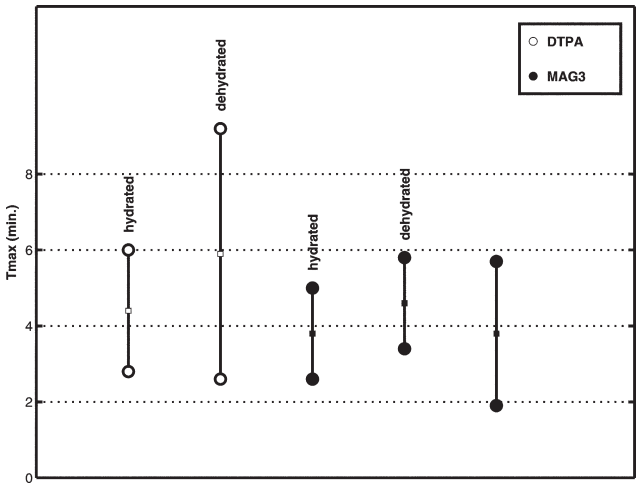

Figure 10 T_{max} normal values (squares indicate mean values and lines show one standard deviation).

for a given kidney when urine flow rate remained constant. However, MTT depends on urine flow rate.[29] According to several clinical studies, hydration state clearly plays a role. However, variation among centers seems to be even more important. Indeed, to test the data analysis among British hospitals, a large intercenter audit was performed and found important variations in the determination of MTT.[81] The committee agreed that MTT has the potential to be robust, but that this potential can only be realized with the development of guidelines for performing the test.

Nondeconvolution Methods (Assessment of Transit Without Measurement of TT)

Because TT measurement has not been an easy task to perform, especially in the early times when computers computed slowly, other approaches were developed in parallel: simpler, more intuitive, and less time-consuming but probably mostly empirical. The simplest of these methods do not take the vascular input function into account so the transit assessed in this way is mixed up with the effect of the input. However, more elaborate methods were devised (NORA and OE) trying to tackle this difficulty. These methods are presented here in an increasing level of complexity.

Visual assessment of images. The simplest way to assess transit is to look at the printed images and assess the quality of drainage.[82] Both the parenchymal transit and the urinary tract transit can be assessed this way. It is probably used by most physicians, at least to get a rough control of the results given by more complex methods. However, it cannot be quantified and it strongly depends on the physician's own experience.

Pelvic appearance time. By looking at the image series, the pelvic appearance time can be determined, which is a parameter of parenchymal transit. This is a very simple and quick method, applicable everywhere. However, this parameter is user-dependent and scaling-dependent. It requires that all images be scaled to the same maximum reference. Tracing a ROI around the pelvis may help to determine this time. Normal values should be around the PTTmin: 1.5 to 5 minutes (90 to 300 seconds) according to the experience of the committee members but references are lacking. When the time reference is taken from the time of first appearance in the cortex instead of the injection time, the normal values are 2.2 ± 0.5 minutes (129 ± 30 seconds).[83]

Visual assessment of curves. This is described in the section "Intrepretation" about diuresis renography.

Time to peak. The time to peak (T_{max}) corresponds to the time of the maximum of the renogram. It represents the point at which tracer outflow (drainage) equals tracer inflow (uptake). It has the advantage of simplicity, except when the renogram stays at a plateau where Tmax may vary much among operators. It proved quite reproducible in the British audit.[81] However, it does not represent a simple physiological parameter. One can only state that minRTT $<$ T_{max}. Therefore, a normal or slightly abnormal T_{max} can be useful to assess normality. It was mostly applied to whole-kidney ROIs so it mostly assesses urinary drainage. Normal values for DTPA depend on hydration (Fig. 10):

- 4.4 ± 1.6 minutes (261 ± 94 seconds) (hydrated)[35] and
- 5.9 ± 3.3 minutes (352 ± 198 seconds) (dehydrated)[35]

And they are slightly lower (by a factor of 1.13 ± 2.22) for MAG3[84]:

- 3.8 ± 1.2 minutes (227 ± 73 seconds) (hydrated)[35];
- 4.6 ± 1.2 minutes (276 ± 71 seconds) (dehydrated)[35]; and
- 3.8 ± 1.9 minutes (225 ± 116 seconds).[85]

Here, the difference between DTPA and MAG3 is mostly due to the higher extraction rate for MAG3 (which entails a faster removal) so this difference lies more in the input function than in the transit itself. With a cortical ROI, Tmax was 2.6 ± 0.5 minutes (156 ± 32 seconds).[85]

Half-Time ($T_{1/2}$). The time to reach a decay of 50% ($T_{1/2}$), although simple in appearance, can have several definitions, leading to different results (Fig. 11)[86]:

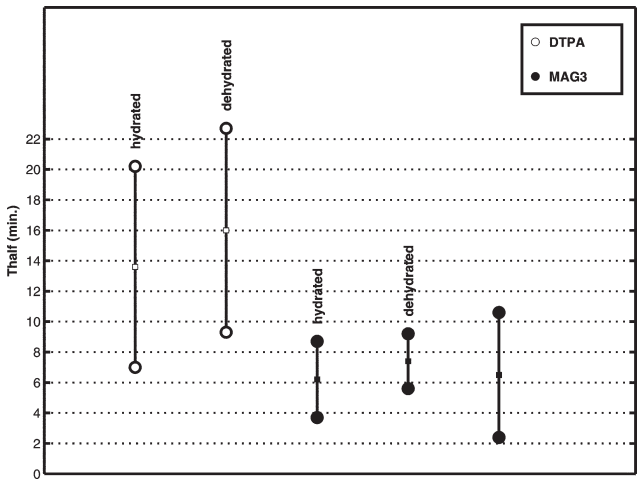

Figure 11 Half-time normal values (squares indicate mean values and lines show one standard deviation).

- delay from a reference time, to reduce activity by 50% and
- half-time taken from an exponential decay fitted on the renogram.

The reference point can be the maximum activity, or for diuresis renography: the time of injection of diuretic, or the time when the response to diuretic is visualized. Without diuretics, normal values ($T_{1/2}$ was defined as the time from the peak to half the peak) for DTPA depend on the hydration state:

13.6 ± 6.6 minutes (814 ± 393 seconds) (hydrated)[35] and 16.0 ± 6.7 minutes (961 ± 404 seconds) (dehydrated)[35]

Normal values for MAG3 are much shorter, which again is mostly related in the difference in the input function due to higher extraction for MAG3:

- 6.2 ± 2.5 minutes (370 ± 148 seconds) (hydrated)[35]
- 7.4 ± 1.8 minutes (446 ± 110 seconds) (dehydrated)[35]
- 6.5 ± 4.1 minutes (392 ± 244 seconds)[85]

NORA. Normalized residual activity is simply defined as the ratio of the renogram value taken at a certain time to the value taken during the second minute (between 1 and 2 minutes after injection, which is shorter than the minimum transit time)[87]:

$$NORA(t) = \frac{\int_{t}^{t+1\,\text{min}} K}{\int_{1\,\text{min}}^{2\,\text{min}} K}$$

Therefore, it can be applied to different times and can be combined with various interventions (condition of stationarity is not required). This versatility has a drawback: comparison between works is made harder because of lack of standardization so when using this index, mentioning the time is mandatory. The most common time for determination is at 20 minutes after injection. The rationale of this index is to scale the remaining tracer to the tracer taken by the kidney. This is clearly better than previous indices (T_{max}, $T_{1/2}$) but some dependence on renal function remains: coefficient of variation under 30% when the clearance of MAG3 exceeds 100 mL/min.[88] This index has the advantages of simplicity and robustness.[89] Proposed normal values (threshold obtained in nonoperated hydronephrotic kidneys) for MAG3 (Fig. 12) were <1.0 for NORA[20] without diuretics.[89] A slightly different index was determined in earlier studies: the ratio of activity at 20 minutes to the activity in the third minute (2-3 minutes). Its normal values depended on the hydration state. For MAG3, they were as follows:

- 0.19 ± 0.03 (hydrated)[35];
- 0.28 ± 0.09 (dehydrated)[35];
- 0.22 ± 0.14[85]; and
- 0.15 ± 0.05 for cortical ROI.[85]

For DTPA, they were higher:

- 0.56 ± 0.16 (hydrated)[35] and
- 0.69 ± 0.22 (dehydrated)[35]

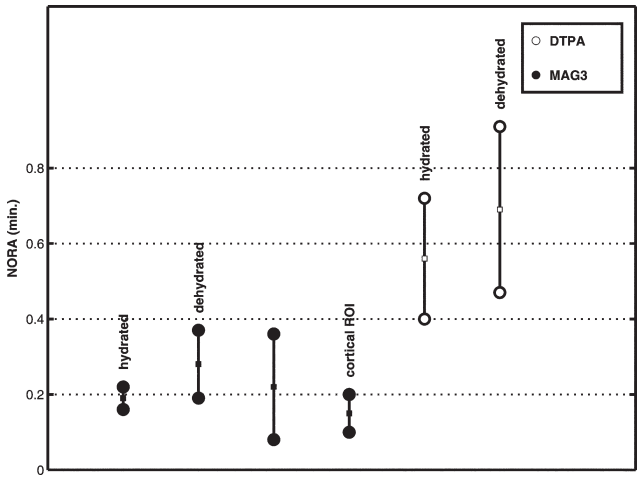

Figure 12 NORA normal values (squares indicate mean values and lines show one standard deviation).

Washout index or excretion ratio or residual cortical activity (RCA). Instead of normalizing the residual activity to activity at a fixed time such as for NORA, other authors suggested to normalize the residual activity against the peak of the renogram.[84,90] The normal value for this index was A_{20}/A_{max} normal <0.3.[91] This index represents urine flow rate and can be recommended as an aid to visual analysis of the renogram.[91] It does not represent however a true assessment of transit time.

Renal output efficiency (OE). Like NORA, renal output efficiency (OE or ROE) was introduced to normalize output to renal function[92] cited by Chaiwatanarat.[93] It is obtained by fitting the integral of the plasma curve $P(t)$ (in practice: corrected heart curve) to the corrected renogram $K(t)$. This gives the total renal uptake:

$$U(t) = B \times \int_{0}^{t} P \qquad (2)$$

where B is a number obtained by the fitting process. By subtracting the remaining activity in the kidney, on can then easily compute the output as a fraction of the uptake.

$$ROE(t) = 1 - \frac{K(t)}{U(t)} \qquad (3)$$

This fitting should be performed before any tracer leaves the ROI, which can be defined as before pelvic appearance, or on the straight part of the Patlak plot, or within a fixed range (1-2 or 1-2.5 minutes). The fitting is made easier by using the Patlak-Rutland plot (the principles of which were introduced by Britton and Brown[94]) or deconvolution both of which giving the multiplication factor for fitting the integral of the blood curve.[13]

MTT and OE are (negatively) correlated but not equivalent nor linearly correlated.[13] The relationship between the two depends on renal function. NORA and OE theoretically have a very strong (negative) correlation.[87,89] They have a very strong correlation to TT when renal function is not too low. OE shows slightly better correlation with MTT than NORA.[87]

Like NORA, OE is versatile, with the same drawback ie, lack of standardization. Here again, we recommend that the time be specified, for instance, ROE(20). This index is slightly less influenced by renal function than NORA but it is not independent of renal function.[13,95] However, correction techniques for this were recently proposed.[96] Also, OE does not take into account that cardiac ROI does not perfectly reflect plasma activity.[59] Normal values were published for MAG3:

- OE (40 minutes) >89% in children[97] after 15 mL/kg hydration and furosemide;
- OE (20 minutes) >86.3 ± 3.7% in normal transplants[75] after furosemide; and
- OE (20 minutes) >81.6 ± 5.4% in normal transplants[76,93] after 500 mL of hydration and furosemide

Other transit indices. Other transit indices were proposed and are detailed in the appendix online.

Interventions

Because transit depends on various conditions, interventions were proposed to change TT: in obstruction, intervention (diuretics) aims at increasing the urinary flow, while in renovascular disease intervention (ACE inhibitors) aims at relieving the vasoconstriction of efferent arterioles. However, because of the need for stationarity in deconvolution, these interventions are usually not associated with measurement of TT but with the simplified transit indices described just above.

Diuresis renography. To assess the effect of a high diuresis, diuresis renography was proposed with probe renography in 1968 by Rado[98] and used in hydronephrosis by O'Reilly in 1978.[99]

Rationale and Pathophysiology. In hydronephrosis, the increased volume of cavities entails lengthening of RTT. The rationale of the test[99,100] was to provoke hyperdiuresis to wash out the cavities. In fact, several phenomena may occur during such a test:

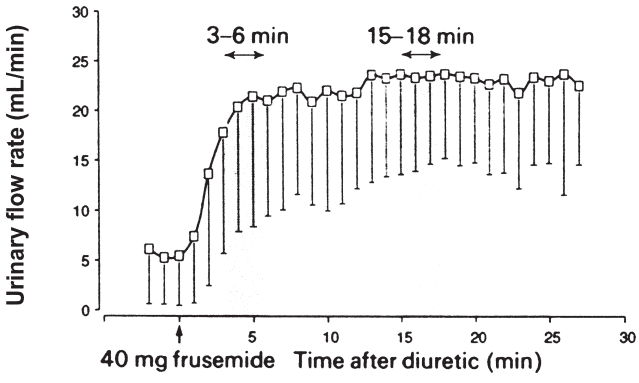

Figure 13 kinetics of the effect of IV injection of furosemide. (Reprinted from Brown et al[28] with permission from Wiley-Blackwell.)

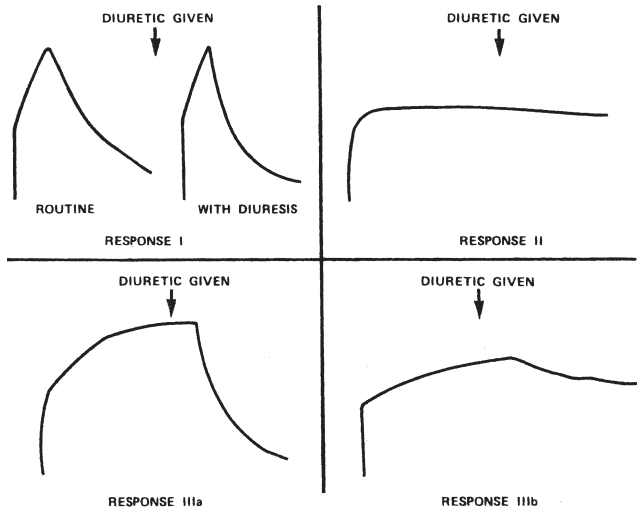

Figure 14 Classical patterns to interpret a diuresis renography. (Reprinted with permission from O'Reilly et al.[100])

- an increase in flow, which shortens the RTT, designed to avoid false-positive results;
- an increase of the cavity volume (nearly doubled in children younger than 2 years[33]), which may give false positive;
- a pyelic distension, which may mechanically increase pyeloureteral resistances, which may reveal true positive[101];
- an increase in flow, which sensitizes the test[101];
- an increase in pyelic pressure[102]; and
- vasodilation.

Protocol. The patient should be well-hydrated (7-10 mL/kg) with a solution with low-content in NaCl (not purely isotonic saline) to ensure a quick diuresis. The oral route suffices. Recommended tracer is MAG3. Furosemide is injected intravenously (1 mg/kg in infants, 0.5 mg/kg in children and 40 mg in adults[39]). In case of renal failure, adapting furosemide dose to the renal function remains controversial.[103-105] The classical time for diuretic administration used to be 20 minutes post injection ("F + 20" protocol). The acquisition should last at least 15 minutes after.

Later on, English and coworkers suggested that injecting the furosemide 15 minutes before radiopharmaceutical ("F-15" protocol) can reduce equivocal responses because maximum diuresis is obtained when the tracer is injected (Fig. 13).[101,106] This would increase the sensitivity and specificity of the test. For simplicity, it was also proposed to inject the radiopharmaceutical and the diuretic simultaneously ("F0" protocol), which is advantageous in case of difficult venous access.[40,107] The respective value of the three protocols is either in favor of F-15,[101,106] some finding more obstructive patterns with F-15 protocol[108] others finding less equivocal results,[109,110] or shows equivalent results for the three protocols.[111,112] The tendency nowadays is to use F0 protocol but this has the disadvantage like the F-15 of not providing information about the baseline state.

Interpretation. Most of the criteria for interpreting diuresis renography were established with the F + 20 protocol. A classical way of interpreting diuresis renography is to look at the curve pattern (Fig. 14). The type IV (Homsy's sign) corresponds to a reascending curve, following initially good drainage, was described as a sign of potential intermittent obstruction, due to the high flow induced by diuretics.[63] First attempt to analyze diuretic renography by quantitative indices was done in 1973[113] with T_{max} and $T_{1/2}$. Normal value for $T_{1/2}$ in diuresis renography is less than 9 minutes[114] or 10 minutes[115] (undetermined between 10 and 20 minutes) Normal NORA is less than 0.23.[89] Normal OE is >78% in adults.[93]

Discussion. This test has some potential pitfalls, as detailed[45]:

- Poor renal function leads to a poor diuresis and impairs the test[116-118] because furosemide-induced flow is roughly proportional to renal function.[28,119] To circumvent this, it was suggested to increase the furosemide dose in case of renal failure[103] but this remains debated.[105]
- A very large pelvis may give a misleading response to diuresis on the renogram, not because of obstruction, but because of a large volume (reservoir effect).[118]
- A full bladder may overlap renal ROI in infants.[116]
- Bad hydration may lead to poor diuresis (diuretics alone do not ensure a good diuresis).
- Bladder fullness can impede drainage.[120]
- Problems with renal immaturity in neonates was suggested[44] but most neonates have an adequate diuretic response.[82]
- Accelerating transit can make the use of Patlak-Rutland method difficult, especially in small children.[121]

It was suggested that diuresis renography had the advantage of testing the urinary tract during pelvic dilation, which may disclose intermittent obstruction that cannot be seen during a baseline test.[122] Paradoxically, patients with large pelves (therefore having bad indices of transit because of the reservoir effect) will accept more easily a high urine load because of pelvis compliance, whereas patients with small pelves may rapidly develop high pelvic pressure, which may lead to function loss. These authors suggest that this enlargement can be considered as a protective mechanism.[33,122,123] Diuresis renography and MPTT assessment provide correlated but not similar results.[124] Very high hydration was suggested by some authors but was questioned about safety[125] and we do not recommend its use.

The Use of Diuresis Renography. With TT Measurements Injection of a diuretic clearly violates the stationarity assumption and is therefore not suitable for pure TT measurement (except if the TT is determined before the diuretic injection). To make diuresis renography and TT measurement compatible requires that the RTT be measured at a time when a plateau is reached in the effect of the diuretic (Fig. 13). This could be either F-15 protocol (RTT is measured when the diuretic effect has reached a plateau) or F + 20 (perform RTT measurement before injecting the diuretic).

Micturition. False obstruction aspects may disappear after micturition.[120,126] Bladder fullness increases renal pelvic pressure in rats[127] and in humans.[128] In case of prolonged transit, it is therefore essential to add images after micturition at the end of the acquisition. This is even more important in patients with a double-pigtail ureteral catheter for whom a pseudoobstructive pattern is common when the bladder is full.[129] An additional argument to perform postmicturition images in the infant is that a huge bladder may often overlap onto the pelvis and give false-positive results. The normal value for postmicturition NORA is <0.1.[89] Renal output efficiency is more difficult to assess after micturition when diuresis is performed (as it is usually) out of the camera: some kind of interpolation is required for the vascular curve for OE.[87]

Gravity-assisted drainage (upright posture). Renography can often show an "obstructive pattern" that normalizes after upright position maneuver.[126,130] Indeed, bladder fullness induces a dilation in pelvicalyceal cavities,[131] maybe because of the anatomical change of the ureteral orifice at the ureterovesical junction.[132] In case of prolonged transit, it is essential therefore to add images after mobilization at the end of the acquisition. However, a question arises: even if drainage is good when the patient is upright, are we certain that the kidneys do not suffer when the patient is lying down eg, during the night?

ACE inhibitors. In renovascular hypertension, a stenosis in a renal artery induces secretion of renin to maintain the filtration pressure by vasoconstriction (induced by angiotensin II) in the efferent artery. The principle of the test is to administer an inhibitor of the angiotensin-converting enzyme system, which relieves the vasoconstriction and induces a drop in glomerular filtration rate. This increases the parenchymal transit time.[41]

Summary

To assess renal transit, two kinds of methods exist. The first one is a measurement of transit time by deconvolution, which was mostly applied to parenchymal transit with DTPA (MAG3 was not introduced until 1986). This measurement provides a parameter that is physiologically relevant (namely, the duration that a molecule stays in the nephron, which is the ratio of the nephron volume to the urine flow). However, a British audit showed a poor intercenter reproducibility of the data processing.[81] The second one is an estimation of transit by several indices, which have no direct physiological significance. Some of them are very simple but in an attempt to get rid of the influence of the input function, two indices were proposed: NORA is the simplest, OE is more complex but depends less on renal function. These simple indices have the advantage of easy reproducibility. However, there is a lack of standardization, especially in the time when these indices should be calculated.

Application of MTT in Clinical Situations

Renal transit was mostly studied in 3 clinical situations: hydronephrosis, renovascular hypertension (RVHT), and kidney transplantation.

Hydronephrosis and Obstruction

Defining hydronephrosis is simple: anatomic dilation of the collecting system, irrespective of the cause.[26] Obstruction is more complex, even though a huge number of papers deal with urinary obstruction. Paradoxically, no universally accepted definition exists for obstruction. Obstructed uropathy can be defined as obstruction of outflow independent of kidney function.[26] Obstructive nephropathy can be defined as renal dysfunction resulting from past or present uropathy. One widely accepted definition for clinically significant obstruction was given by Koff: "Any restriction to urinary flow that, left untreated, will cause a progressive renal deterioration"[133] with its variant ". . . limiting the functional potential of the developing kidney."[134] This definition is relevant to clinical practice because it indicates which patients may benefit from surgery. However, it has the drawback of being retrospective and not easy to assess because of ethical considerations. To be certain about a patient's obstruction requires seeing his/her renal function deteriorate! If the patient is preemptively operated, it will become impossible to know if the function would have decreased if surgery had not been performed. With such a definition, no test will give a diagnosis of obstruction, only a correlation with the potential for progressive renal deterioration.[122] Moreover, concentrating ability would be a better marker of renal function than glomerular filtration rate in these patients[135,136] Lack of a simple gold standard makes the assessment of the utility of transit times very difficult. The clinically relevant questions could be formulated as follows:

- If kidney is not operated, will its function deteriorate?
- If kidney is not operated and function is preserved, will it be at the cost of a compensatory mechanism?
- If function decreases and kidney is operated, will function recover?
- What is the long-term prognosis of unoperated patients?

After complete acute obstruction, renal function deteriorates within a few hours and recovers after relief if it does not last more than a few days.[137] The situation is quite clear-cut and isotopes are rarely required. Therefore, here, only partial or intermittent obstruction will be considered. In fact, hydronephrosis probably encompasses many distinct diseases and at least two clinical conditions should be distinguished: neonatal hydronephrosis and adult hydronephrosis (even if the adult hydronephrosis may in some cases be the result of neonatal hydronephrosis). More complexity can be added when one considers that obstruction may be intermittent. In this case, any test performed outside the period of obstruction will remain normal.[63] Also, one of the problems in follow-up is that renal dysfunction can be induced by other renal diseases (such as infection).

Pathophysiology and Animal Models

An important part of the knowledge of obstruction pathophysiology comes from animal models, with the reservation that they cannot necessarily be transposed to humans. The sequence of events leading to renal damage is not fully understood but appears to result from increased pressure with reduction in renal blood flow.[116] Acute obstruction results in increased pelvic pressure and a decreased renal blood flow.[138] Though it appears reasonable that increased pressure is the cause of renal damage, during chronic dilation, baseline pressure is only marginally (if even) elevated and cannot be used as a diagnostic criterion.[139-142] Others have suggested that obstructive damage may be due to renal ischemia.[143] Pelvic volume in itself would not necessarily be a pejorative criterion and hydronephrosis could even be seen as a mechanism to protect kidney from pressure increase.[144] After increasing ureteral pressure in rats by 25 to 40 mm Hg, Rector and coworkers observed a reduction in GFR by 20 to 37% with an increase in tubular fluid reabsorption, an enlargement in tubular volume by 23% to 56% and an increase in tubular transit time by 67% to 245%.[145] This increase in tubular TT therefore seems to be caused by both a reduction in flow and an increase in volume, making it a theoretically sensitive parameter in this animal model. However, in congenital ureteropelvic junction obstruction, the tubule volume is not increased (and may even be decreased),[146,147] proximal tubules being decreased in length and smaller in sectional area while distal tubules are unchanged. An increase in MWKTT as well as in MPTT was observed in experimental obstruction with a correlation between MPTT and the pelvic baseline pressure.[148] However, the level of "obstruction," as assessed by the renal scan, was not correlated with renal function loss.[149] In an animal model, T_{max} and MTT were sensitive for diagnosis of obstruction but they lacked specificity.[150] A nonobstructive (grade I) pattern though seems a good indicator of an unobstructed pelvis.[151] It must be emphasized here that patients with dilated but unobstructed cavities may have transit times larger than normal.

Surrogate Gold Standards

The Whitaker test. The Whitaker's test was proposed as early as 1969 by Johnston,[140] then published in 1973, without any true validation in the original paper[152] nor afterward[25,153,154] This test consists of infusing the pelvis with a constant flow of 10 mL · min^{-1} while measuring the pelvic pressure. It could be performed either by a nephrostomy tube or by percutaneous puncture. The rationale of this test is that an elevated pressure is the cause of renal damage in obstruction. If the pelvic pressure exceeds the bladder pressure by at least 22 cm H_2O, the test is considered positive ("obstructed"). If it remains $<$15 cm H_2O above the bladder pressure, it is considered normal. Between the two, it is considered equivocal. The flow rate of 10 mL · min^{-1} is in the upper range of physiological final urine flow for both kidneys so it may be nonphysiological for one single kidney taken separately.[122] In medicine, independent (intensive in physics)

variables include pressure, temperature, concentration (they are unrelated to body size) and do not need any scaling (such as temperature/kg). Volumes, masses, amounts and flows are dependent (extensive in physics) and need adjustment for size (plasma volume/kg) to define normal values across populations, so adapted flows were alternatively proposed especially for children.[155] It had the advantage over diuresis renography of independence of renal function. However, it is invasive and has morbidity.[25] This test may be hindered by leakage around the intrapelvic catheter. In one study, no correlation was found between the pressure study and the functional outcome of surgery.[156] This test has now been abandoned in most countries.[141,157-161]

Surgical or pathological finding. Histopathological changes can be found in hydronephrosis.[162,163] However, no proof exists that these changes are primary or secondary,[164] nor that they entail a poor prognosis, so their value is still not clear.

Clinical Situation

Antenatally discovered hydronephrosis is not a rare condition, occurring in about 1/500 pregnancies.[165,166] After the advent of systematic antenatal ultrasound tests, there was a major increase in diagnosis of dilated pelvis in infants. Initially, it was recommended that all these infants would be operated.[167] Then, the Whitaker's test and diuresis renography were considered as criteria for operation. It was later shown that most newborns with severe unilateral hydronephrosis can be safely managed conservatively at least when relative function of the dilated side exceeds 40%.[159,168-173] When initial function is <40%, operation results in an improvement of relative function[171] but even with function <40%, the majority of patients recovered function spontaneously in two series.[169,174] A randomized, prospective study also showed that even if pyeloplasty did improve the grade of hydronephrosis and the renographic pattern, function was not significantly different in the operative group than in the conservative group.[175] Other studies suggested the same conclusion.[176] Some retrospective studies however suggested higher risk with conservative management.[177-181] It is still not clear whether early operation results in a better functional prognosis[178,180] or not.[176,182,183] The tendency nowadays is to concentrate on function, not on transit. A logistic regression analysis suggested that deconvolution techniques helped less than standard renography to differentiate normal from acutely obstructed patients.[184] However, this study used a 20-second frame duration (which is now considered as too long for deconvolution). The PTTI was not tested here.

Role of Transit Assessment

Estimation of the usefulness of transit time in hydronephrosis is made very difficult by the lack of a gold standard: many clinical studies were published in the last 30 years but, in most of them, criteria for obstruction were not even clearly defined. When criteria were defined, they were acceptable only in a few cases. In the other cases, diagnostic criteria either included the results of the renal scan (which results in a self-fulfilling prophecy), used the results of nonvalidated procedures (such as the Whitaker's test or other transit indices) or showed a postoperative improvement in a transit index but not in the patient's condition (volume reduction from pyeloplasty intrinsically accelerates transit) nor on the level of renal function.[33] The potential of transit assessment is twofold: TT assesses obstructive nephropathy, whereas diuresis renography assesses urodynamics.[39] Probably, even without any obstruction, hydronephrosis induces urine stagnation, which can be assessed by transit time and increases the risks of infection as well as urolithiasis.[25]

Pathological findings. In a short series of patients, response to renography was shown to correlate with the presence of pathological changes.[185] The visual analysis of the renogram was correlated with histopathological changes in the upper urinary tract.[186] However, the clinical significance of these pathological changes remains uncertain.

Whitaker's test. As the Whitaker's test was once considered a gold standard, many studies compared transit parameters to this test and generally found correlation but not equivalence.[102,162,187-191] Diuresis renography was discordant with Whitaker's test in patients with poor renal function and very large pelves.[192] Discrepancies between diuresis renography and the Whitaker test may be due to the flow rate differences (in some cases, hyperdiuresis may give flows higher than 10 $mL \cdot min^{-1}$).[193] PTTI was highly correlated with the Whitaker's test results.[16] For operated patients, PTTI was normalized after surgery.[16]

Negative predictive value of fast transit. In a large multicentric study, acutely obstructed adults and chronically obstructed children had a significant increase in MTT.[19] A negative diuresis test seems to be associated with a good prognosis without surgery.[100] In a prospective study, when a child presented with hydronephrosis, diuresis renography was performed (with a huge fluid load of 4% BW and 0.3 mg $\cdot kg^{-1}$ furosemide) and patients were operated if the renogram had an "obstructive" shape; result was an overall increase in relative renal function after operation and stability without operation; only 2 children (6%) initially classified as "non obstructed" required operation later.[194] Similar results were found retrospectively by others in children.[82] A good-drainage diuresis renography is generally recognized as an acceptable criteria for the absence of obstruction in children[40] but also in a global population,[39] though intermittent obstruction could result in false-negatives. Sufficient data therefore support the consensus that normal transit parameters have a good negative predictive value.

Positive predictive value of slow transit In a small series, MWKTT paradoxically increased in as many cases as it decreased after pyeloplasty[195] in pediatric patients with highly dilated systems, but without obstruction on simple follow-up, 43% were false-positive using MWKTT with DTPA and a threshold of 5 minutes.[74] Diuresis renography was unable to predict which children would undergo surgery in a prospective trial of conservative management.[168,169,171] An extensive metananalysis review of the literature was published in

2002,[196] concluding that among the 474 children for whom it was decided to follow up without surgery, 10% crossed over to surgery (mostly for decrease in function or increase in pelvic volume) and only 3 kidneys (0.6%) significantly lost function. Diuresis renography wrongly identified "obstruction" in 87% of these kidneys. This suggests that the positive value of an 'obstructive' diuresis renography pattern is extremely poor. However, doubts remain about the long-term prognosis of these nonoperated children.[161]

Summary on Obstruction

TT may be useful in obstruction. Obstruction remains difficult to define in a given patient and no gold standard exists. Therefore, the evaluation of the role of transit time assessment in obstruction remains debated, without proven evidence. A normal transit assessment probably has a good negative predictive value. On the contrary, no criteria are universally accepted, which allow interpretation of impaired drainage as obstruction[40] and we still lack a properly-designed prospective study assessing the value of radionuclides in hydronephrosis.[197] So, at least in children, in hydronephrosis it is not the type of transit test (sophisticated or not) which is the real question, but if a slow transit (regardless of the method) has a positive predictive value.

Renal Artery Stenosis and Renovascular Hypertension

In 1963, Dore suggested that transit time studies could be useful in renovascular hypertension (RVHT).[4] Renovascular hypertension is generally due to renal artery stenosis. However, most of patients with renal artery stenosis do not have RVHT. The main criterion for RVHT is relief of hypertension after revascularization and renal artery stenosis can be proved by arteriography. Gold standards do exist here and the case is therefore much simpler that for hydronephrosis.

Hemodynamically Significant Renovascular Hypertension

As explained in "ACE Inhibitors," a main issue is to assess an increase in transit times after administration of ACEI. An increase of Tmax of more than 5 minutes or an increase of MPTT of more than 20% after ACEI were predictive of success after revascularization.[198] A multicenter study showed that T_{max} or curve pattern analysis performed well in diagnosing RVHT.[199] An increase in A_{20}/A_{max} of more than 0.19 (for OIH) or 0.22 (for DTPA) was a sign of RVHT.[200]

In the SNM procedure guideline for diagnosing renovascular hypertension, a 0.15 change in A_{20}/A_{max} ratio (ie, an increase from the 0.30 normal upper limit to at least 0.45) was considered significant, an increase between 0.1 and 0.15 being considered borderline.[91] In the same guideline, the use of T_{max} was suggested (positive with increase of at least 2 minute or 40%). The visual interpretation of the curve was suggested (positive if change in renogram grade). The use of parenchymal transit time measurement was recommended if available, without criteria. An increase of at least 2 minutes in the pelvic appearance time was also considered as positive.[41] Even without pharmacological intervention, baseline transit was proposed to diagnose RVHT: increased MPTT[67] or PTTI (improperly called PTT in their paper)[79] would be a criterion for RVHT. A prospective study provided evidence for predictive ability of DTPA MPTT.[68] MTT would also be useful to select patients with renal failure that can benefit from ACE inhibitors (when MTT does not increase with this drug). Tmax would not provide the same information but data were not presented.[201] We can conclude that transit assessment has a proved utility in this indication but that simple parameters perform as well as true TT measurement.[202] One potential interest of TT is to provide a number, which makes interpretation and intercenter comparison easier to perform.

Renal Artery Stenosis

Rutland and coworkers suggested that transit time assessment alone could diagnose renal artery stenosis. However, the thresholds were determined retrospectively.[203] Others also proposed to use increased MPTT as a criterion to diagnose RAS without pharmacological intervention.[65] The majority of studies compared baseline transit to transit after ACEI. It was shown that an increase of MPTT of more than 20% or an increase of Tmax of more than 5 minutes after ACEI is predictive or renal artery stenosis.[198,204] However, visual inspection of the renogram performed as well in diagnosing renal artery stenosis during the ACEI test.[205] One study has shown better correlation with the degree of stenosis for the SDTT than for the T_{max}.[18] Others found no advantage of deconvolution techniques over simple renogram analysis in this indication.[206] Here again, transit assessment has a proven utility but no superiority was found for TT measurements over simple indices.

Assessment of Transplanted Kidneys

Transplanted kidneys are at risk for many disorders, especially in the first days after transplantation, including ischemia, acute rejection (AR), acute tubular necrosis (ATN), and obstruction. The gold standard is here not so easy to define. However, the evolution under treatment of these acute disorders usually permits reliable diagnosis. Vascular transit would have a role in differentiating AR from ATN. ATN would have normal VTT, whereas all other transplant disorders (especially AR) would have increased VTT.[14] However, in this study, thresholds were determined retrospectively. This utility was supported by another study.[27]

Parenchymal transit time was able to separate ATN or AR from normal (but so did pelvic appearance time) but it did not separate ATN from AR.[72] Another retrospective study showed contradictory results comparing MTT in outer and middle regions.[69] In transplants, obstruction is usually acute so diagnosis is much easier than discussed above (rapid and significant decrease of plasma creatinine after drainage, without other confounding cause). A few studies suggested that transit assessment is useful to differentiate obstructed from normally functioning transplants using either MWKTT[207] or diuresis renography: in transplants without obstruction, after furosemide, OE was above 77% with MAG3.[75] Using a cut-off of 75% (20 minutes diuresis F + 10) gave a sensitivity/specificity of 92%/87% in diagnosing obstruction.[76]

Miscellaneous

In case of a poor injection (eg, partially subcutaneous injection), the renogram cannot be interpreted. However, the RRF can still be determined and is very similar to the RRF obtained in the same patient after a proper IV injection[208,64] Long renal transit time indices in patient without renal disease would give a pejorative prognosis of developing renal insufficiency after cardiac transplantation in patients without previous renal disease.[209] Mean transit times were significantly higher in a large series of patients with vesico-ureteral reflux (even after operation).[19] No explanation was provided but one could postulate a dilation of tubules. A dilated collecting system such as seen in grade III- V reflux, or even a reflux phenomenon occurring during the renogram might be falsely interpreted as an increase of transit time.

Conclusion

Purest transit parameters (measured transit times) can be obtained by deconvolution but they lack intercenter reproducibility. Simple parameters are more influenced by the input function and do not reflect truly physiological parameters. Moreover, transit is affected by many parameters (hydration state, arterial pressure, reservoir effect, full bladder, posture, etc) More standardization is therefore desirable for both classes of methods. In obstruction, no consensus was reached among the committee members. The majority think that no clinically relevant utility of transit assessment is proved, except probably a normal transit, which can be assessed by any method and has a good negative predictive value. Some other members think that transit assessment is useful in the diagnosis of obstruction. In transplant assessment and RVHT, transit is useful but there is no proof that exact transit time determination is clinically more relevant than using simple transit indices.[40] To progress in the technical aspects of assessing renal transit, things could go in 4 steps:

- Standardization of procedures for a few parameters (eg, MPTT and PTTI, NORA and OE in diuresis renography); pressure on manufacturers would also be needed to provide user-friendly software
- International audit to assess the intercenter reproducibility with a database of blinded studies (for this, it would be needed to construct a global database to which different centers may contribute data acquired to agreed specifications). Both data acquisition under standardization (hydration, etc) and post processing could thus be assessed. In children, it would be important to have a database of assumed "normal kidneys" (the contralateral side of abnormal kidneys). The second important database should be the group of dilated kidneys for which obstruction is unlikely: for instance the residual dilation after pyeloplasty or the major vesicorenal reflux.
- Multicenter determination of normal values under standardized conditions
- Prospective multicenter assessment of clinical usefulness of these measurements, with well-defined gold standard (eg, a randomized prospective study in functionally symmetric kidneys using transit as operation criterion). The methodology should be validated beforehand by specialized statisticians.

Appendix

Available online at http://www.ISCORN.org.

Note on References

Only peer-reviewed papers were considered for clinical evidence, not editorials, letters, abstracts, books, or personal communications. Other papers have be taken as useful for their ideas but not for clinical or experimental evidence. The quoted references were classified along the following categories[210,211] (we must however remark that this classification was designed for therapeutic studies, not for diagnostic studies as here). Additional categories were used to adapt the original categories to the specific nature of transit assessment. The levels of evidence were:

- C1 = Level I (at least one properly randomized controlled trial)
- C2-1 = Level II-1 (well-designed controlled trials without randomization)
- C2-2 = Level II-2 (well-designed cohort or case-control analytic studies, preferably from more than one center or research group)
- C2-3 = Level II-3 (multiple time-series with or without intervention; dramatic results in uncontrolled experiments could also be regarded as this type of evidence)
- C3 = Level III (opinion of respected authorities, based on clinical experience, descriptive studies or reports of experts committees)
- U = Studies that were uncontrolled, retrospective or otherwise failed to fulfil the previous criteria (note that prevalidation studies where threshold was determined retrospectively are classified here)
- M = Mathematical evidence
- O = Opinion/Review
- P = Physiological data
- A = Animal model
- N = Numerical simulations
- B = Book
- L = Letter
- S = Survey
- R = Abstract

The article category is noted at the end of each reference.

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