VIA MEDICA

Nuclear Medicine Review 2002
Vol. 5, No. 2, pp. 105–108

ISSN 1506–9680

Original

Optimal time window for measurement of renal output parameters

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[Received 3 IX 2002; Accepted 15 XI 2002]

Abstract

Although normalised residual activity (NORA) and output efficiency (OE) are usually measured at a fixed time *t*, their dependency on *t* may affect the prediction of mean transit time (MTT). This study aimed to evaluate their degree of dependency on *t* and to determine an optimal time of measurement by assessment of their relationship with MTT for various times *t*. A simulation model generated 232 cortical renograms by convolving one plasma disappearance curve with 232 created cortical retention functions.

The results show that considerable changes are observed for NORA and OE , depending on the time of measurement *t*. The choice of this time significantly influences the predictive value of these parameters for estimating MTT. The optimal time for measurement of NORA and OE should be close to the MTT, at the moment when emptying takes place. In the clinical practice, it should be adapted to the clinical problem under investigation.

Key words: renography, output efficiency, NORA, simulation study

Introduction

Transit time evaluation is a controversial issue in nephro-urology [1, 2]. Several methods have been described, each with its advantages and disadvantages [3, 4]. Two renal output parameters might be useful in this context, namely normalized residual activity (NORA) and output efficiency (OE). One of the major advantages of these variables is linked to the fact that they allow estimation of the renal outflow at any time *t* of the renogram, either after the furosemide test or after the post micturition image [5, 6]. This advantage could however become a disadvantage. Indeed, as the values of NORA and OE are dependent on the time of measurement *t*, the choice of *t* may affect the predictive value of these parameters. It is possible that for a given *t*, OE and NORA are closely related to mean transit time (MTT), while for other values of *t* these parameters are insensitive to variations of MTT. For instance, whatever the real value of MTT, OE and NORA are useless if calculated three minutes after the start of the renogram, since no renal output would be observed in all cases. They are also useless if calculated twenty-four hours after the renogram, as total emptying would have occurred in all kidneys.

However, despite the obvious dependency on *t*, the recent EANM guideline on renography [7] suggests that residual renal activity after furosemide and micturition may be acquired at any time within 60 min after injection of the tracer and regardless of the time of furosemide administration.

The aims of this study therefore were firstly to evaluate the degree of dependency on *t* of OE and NORA, and secondly, for various time *t*, to assess the relationship between these parameters and MTT, in order to determine an optimal time *t* at which to calculate these transit parameters.

Material and methods

A series of cortical renograms $R(i)_m$ were generated in a computer simulation model by convoluting one input function *P(i)* with *m* different cortical retention functions $H(i)_m$ in accordance with the equation:

$$R(i)_m = P(i) \times H(i)_m \qquad \text{(Eq. 1)}$$

which, for discontinuous sampling methods can be written as:

$$R(i)_m = \sum_{j=0}^{i} P(i).H(i-j)_m \qquad \text{(Eq. 2)}$$

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with *i*, the frame number, running from 1 to *N,* the total number of frames.

Time per frame and number of frames *N* were set at 10 s and 720 respectively, resulting in a theoretical acquisition of 120 min.

As input function *P(i)* served the plasma disappearance curve of the renal tracer, which for discontinuous sampling methods can be simplified as:

$$P(i) = \alpha_1 . e^{-i.\lambda_1} + \alpha_2 . e^{-i.\lambda_2} \qquad \text{(Eq. 3)}$$

The values α_1, α_2, λ_1 and λ_2 were derived from a plasma disappearance curve of ^{99m}Tc-MAG$_3$ obtained in a patient with reduced renal function: α_1 = 19.39% ID/l, α_2 = 2.98% ID/l, λ_1 = 155.03 10^{-3}/frame and λ_2 = 1.65 10^{-3}/frame; these values correspond to a clearance of 196 ml/min.

The cortical retention functions were created in four phases. Phase 1: The mean transit time (MTT) of the retention function was set between 3 to 60 min, increasing with 1-min steps. Phase 2: For every value of MTT, the ratio of the minimal transit time (MinTT) to MTT was arbitrarily fixed at 0.80. In this model we have disregarded the vascular phase, *H(0)* is therefore equal to 1. Phase 3: For every value of MTT, one retention function was created in a spreadsheet program (Microsoft Excel) reflecting a multi-nephron model with a linear increase in transit time (Fig. 1A). Due to the linear increase in transit time, the ratio of maximum transit time (MaxTT) to MTT was equal to 1.20. Phase 4: Three variants of this cortical retention function were also created; all had a non-linear increase in transit time. The ratio of MaxTT to MTT ranged from 1.11 to 1.18 for the first (Fig. 1B), from 1.30 to 1.60 for the second (Fig. 1C) and from 1.61 to 1.99 for the third (Fig. 1D).

In this way, for each MTT value, 4 different shapes of cortical retention curves reflecting a multi-nephron model were created, resulting in a total of 232 retention functions with MTT between 3 and 60 min and corresponding renograms. In each of the created cortical renograms, NORA and OE were calculated for *t* equal to 10, 20, 30, 40, 50 and 60 min.

NORA$_t$ is defined according to the formula:

$$NORA_{t,m} = \frac{R(i_t)_m}{R(i_{t=2})_m} \qquad \text{(Eq. 4)}$$

$R(i_{t=2})_m$, the renal cortical activity at 2 min, was calculated as the sum of frames 7–12; likewise the renal cortical activity $R(i_t)_m$ at *t* equal to 10, 20, 30, 40, 50 and 60 min was calculated respectively as the sum of frames 55–60, 115–120, 175–180, 235–240, 295–300 and 295–300.

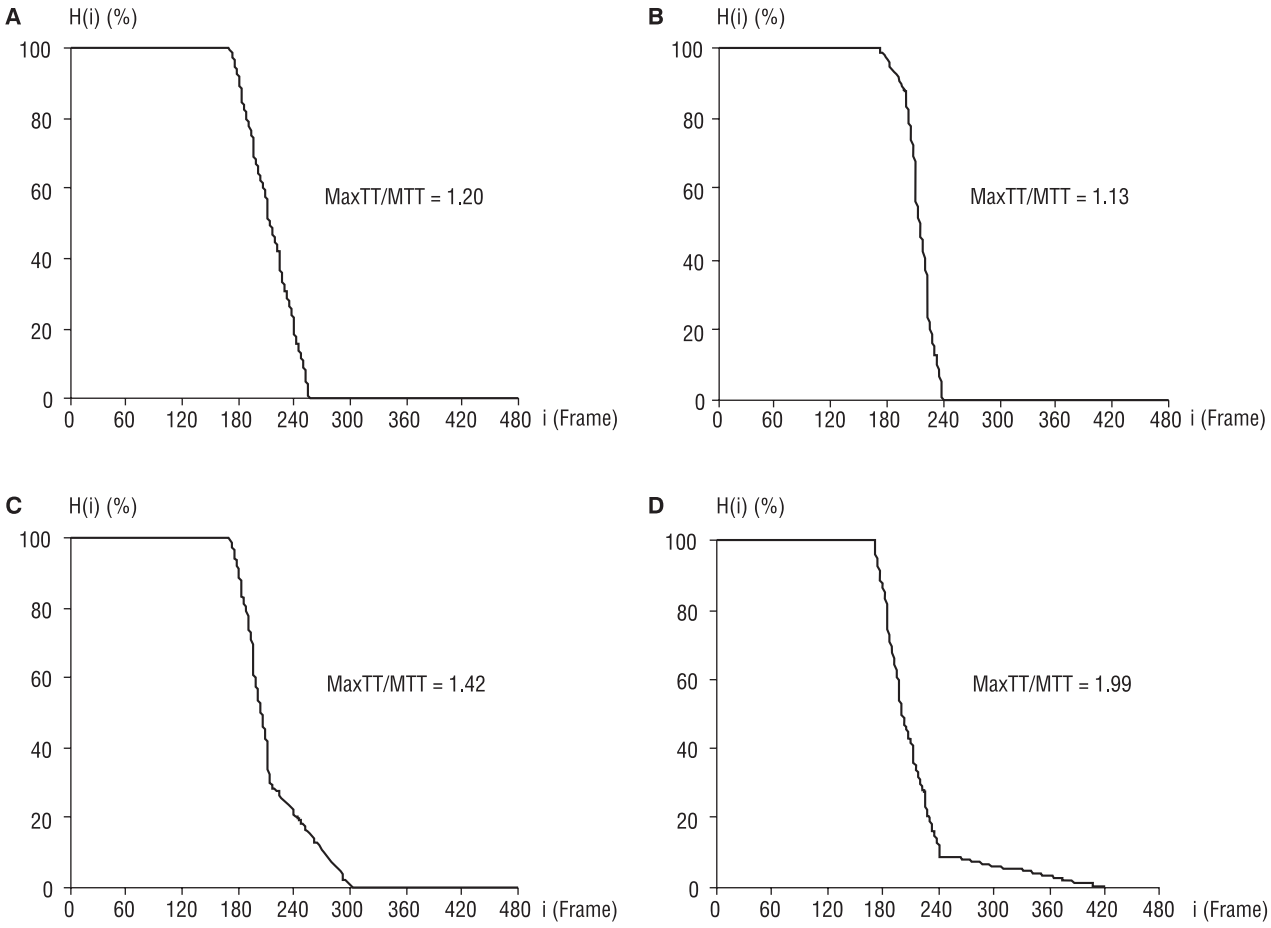

Figure 1. Examples of different shapes of cortical retention functions. For all of them, MinTT and MTT are equal to 29 min and 39 min respectively. The first model (**A**) is based on a linear increase of transit time and the ratio of MaxTT to MTT is therefore 1.20. The second model (**B**) is based on a non-linear increase of transit time, with the ratio of MaxTT to MTT fixed between 1.11 and 1.18. The third and the fourth model (**C** and **D** respectively) are based on a non-linear increase of transit time with the ratio of MaxTT to MTT respectively fixed between 1.30 and 1.60 and between 1.61 and 1.99.

OE_t is defined as the ratio of total output and total input at time *t*:

$$OE_{t,m} = \frac{\text{Total output for } R_m \text{ up to } t}{\text{Total input of } P \text{ up to } t}$$

which, expressed as a percentage, equals:

$$OE_{t,m} = 100\% \times [\frac{\sum_{t=0}^{t} P(i_t) - R(i_t)_m}{\sum_{t=0}^{t} P(i_t)}] = 100\% \times [1 - \frac{R(i_t)_m}{\sum_{t=0}^{t} P(i_t)}] \quad \text{(Eq. 5)}$$

The renal cortical activity $R(i_t)_m$ was calculated in the same way as that for NORA. The relationship between MTT and the transit parameters $NORA_t$ and OE_t was determined graphically.

Results

This study shows (Fig. 2) however that the degree of variability of OE at different times *t* is considerable. For example, for MTT equal to 30 min, OE_{40} is about 51% whereas OE_{60} is 78%. Moreover, the predictive value of OE_t for MTT is significantly influenced by the range of MTT investigated (Fig. 2). For values of MTT between 3 to 20 min, changes in OE_{20} closely reflect the modification of MTT. In this range of MTT, OE_{20} is therefore highly predictive of the value of MTT. The predictive value of this parameter is somewhat raised if the MTT of the kidney studied is less than 20 min OE_{60}, on the other hand, varies only slightly (from 100% to 88%) when MTT rises from 3 to 20 min, thereby suggesting a much lower predictive value of this parameter. The contrary is observed for MTT ranging from 30 to 50 min In this instance, OE_{20} totally looses its predictive value as in all cases OE_{20} equals 0%, whereas OE_{60} closely follows the changes in MTT. In this range of MTT, OE_{60} is highly predictive.

Similar patterns are observed for NORA (Fig. 3). Important variation of NORA is observed, depending upon the time at which this parameter is measured. For example, for MTT equal to 30 min, $NORA_{20}$, $NORA_{40}$ and $NORA_{60}$ equal 4.2, 4.1 and 1.9 respectively. The predictive value of NORA for MTT is also significantly influenced by the range of MTT investigated. For a value of MTT of less than 20 min, $NORA_{20}$ has the highest predictive value, whereas $NORA_{60}$ is best suited for values of MTT ranging from 30 to 50 min.

Discussion

Both NORA and OE have been proposed for the measurement of renal transit, and the calculation of these renal transit parameters at fixed times is in common usage [7, 8]. The time chosen is usually circumstantial such as the end of renogram, end of furosemide acquisition or after micturition [5, 8]. The recent EANM guideline on renography [7] suggests that this parameter may be measured at any time within 60 min after injection of the tracer.

On theoretical grounds however this guideline is questionable, as these parameters are dependent on the time *t* at which they are measured. The magnitude of this time-dependency should first be studied in order to ascertain the validity of the guideline.

We have chosen to evaluate the degree of this dependency by a computer-simulated model rather than on patient's data, the rationale for this being firstly that a computer model is not hindered by such factors as noise, background and uncertainties related to the determination of MTT. Secondly, such a model allows the creation of a broad range of values of MTT and shapes of retention function. Thirdly, such a model allows a more accurate evaluation of OE on the postmicturition image by calculating the denominator of eq. 5 instead of estimating by extrapolation the total input of *P* up to the time of measurement *t*. As illustrated in the results of the present study, NORA and OE should be measured at the moment when emptying takes place and neither before emptying has started (before MinTT) nor after the cortex of the kidney has been emptied. Therefore, contrary to what is sug-

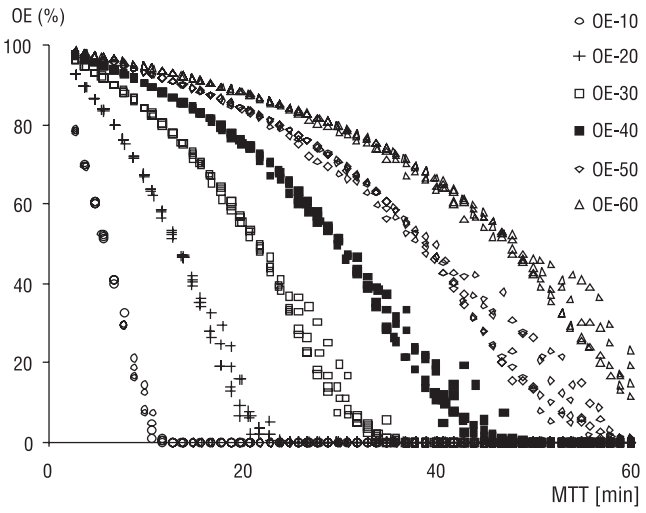

Figure 2. Relationship of OE_t and MTT for various values of *t*. For OE at $t = 10$ min (OE-10), a close relationship exists with MTT for values up to 10 min; for all values of MTT higher than 10 min, OE-10 remains 0%. For OE at $t = 40$ min (OE-40), a close relationship exists with MTT for values up to 30 min; for the values of MTT between 30 min and 50 min, the relationship with OE-40 becomes dispersed and for values of MTT higher than 50 min, OE-40 remains 0%.

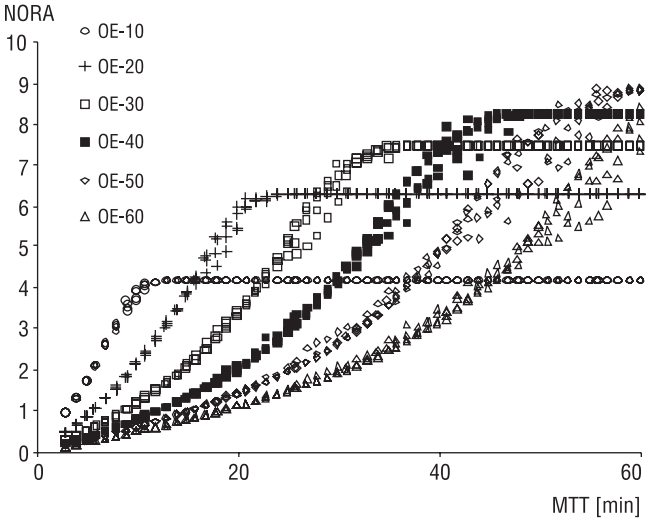

Figure 3. Relationship of $NORA_t$ and MTT for various values of *t*. For NORA at $t = 10$ min (NORA-10), a close relationship exists with MTT for values up to 10 min; for all MTT values higher than 10 min, NORA-10 remains unchanged. For NORA at $t = 40$ min (NORA-40), a close relationship exists with MTT for values up to 30 min; for values of MTT between 30 min and 50 min, the relationship with NORA-40 becomes dispersed and for values of MTT higher than 50 min, NORA-40 remains unchanged.

gested [7], OE and NORA should not be determined freely at any time within the 60 min after tracer injection. The choice of time *t* for measuring NORA and OE should be based on the range of the expected MTT of the kidney investigated. In a captopril study for example, one is usually faced with a normal or only slightly abnormal renogram before administration of the drug, and in the case of renovascular hypertension, the administration of captopril will induce a longer renal transit. In this application, OE or NORA should be calculated quite early on, and OE_{20} or $NORA_{20}$ are likely to be good parameters. Late OE or late NORA will have a lower predictive value for MTT. When evaluating renal transit in a kidney with dilated cavities, OE and NORA should be determined at a later time. Indeed, in these cases the focus is on separating cases with prolonged transit time (non-obstructed dilated cavities) from those with a much longer transit (obstructed kidneys). The optimal time for measuring OE or NORA in these circumstances cannot be determined by this simulated study and should be based on clinical data. Based on a preliminary analysis, the optimal time may be considerably longer than 1 hour.

The situation differs with the administration of furosemide, since the diuretic significantly shortens the renal transit. The timing of furosemide administration is critical. The optimal time for measuring OE and NORA should be earlier when furosemide is administered with the tracer (F0) or before (F–15), and later if given after (F+20). Again, the optimal times for measurement of these variables are still to be determined, based on clinical studies. In the case of dilated renal systems, the optimal time is estimated at around 30 min for the F0 and around 50 min for F+20.

Conclusions

This study shows that considerable changes are observed for NORA and OE, depending on the time of measurement *t*. The choice of this time significantly influences the predictive value of these parameters for estimating MTT. The optimal time for measurement of NORA and OE should be close to the MTT, at the moment when emptying takes place. In the clinical practice, it should be adapted to the problem under investigation. Further clinical studies are recommended for the determination of the specific optimal time for each medical application.

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