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Modification of a two blood sample method used for measurement of GFR with 99mTc-DTPA

Marian J. Surma[1], Anna Płachcińska[2], Jacek Kuśmierek[1]

[1]Department of Nuclear Medicine, Medical University in Łódź, Poland
[2]Department of Quality Control and Radiological Protection, Medical University in Łódź, Poland

Abstract

BACKGROUND: Measurements of GFR may be performed with a slope/intercept method (S/I), using only two blood samples taken in strictly defined time points. The aim of the study was to modify this method in order to extend time intervals suitable for blood sampling. Modification was based on a variation of a Russel et al. model parameter, selection of time intervals suitable for blood sampling and assessment of uncertainty of calculated results.

MATERIAL AND METHODS: Archived values of GFR measurements of 169 patients with different renal function, from 5.5 to 179 mL/min, calculated with a multiple blood sample method were used. Concentrations of a radiopharmaceutical in consecutive minutes, from 60th to 190th after injection, were calculated theoretically, using archived parameters of biexponential functions describing a decrease in 99mTc-DTPA concentration in blood plasma with time. These values, together with injected activities, were treated as measurements and used for S/I clearance calculations. Next, values of S/I clearance were compared with the multiple blood sample method in order to calculate suitable values of exponent present in a Russel's model, for every combination of two blood sampling time points. A model was considered accurately fitted to measured values when SEE $\leq$ 3.6 mL/min. Assessments of uncertainty of obtained results were based on law of error superposition, taking into account mean square prediction error and also errors introduced by pipetting, time measurement and stochastic radioactive decay.

RESULTS: The accepted criteria resulted in extension of time intervals suitable for blood sampling to: between 60 and 90 minutes after injection for the first sample and between 150 and 180 minutes for the second sample. Uncertainty of results was assessed as between 4 mL/min for GFR = 5–10 mL/min and 8 mL/min for GFR = 180 mL/min.

CONCLUSIONS: Time intervals accepted for blood sampling fully satisfy nuclear medicine staff and ensure proper determination of GFR. Uncertainty of results is entirely acceptable and for high GFR values even comparable with uncertainty of multi-sample measurements.

KEY words: GFR, two-sample method, slope/intercept GFR

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Background

Renal clearance is a measure of renal efficiency in elimination of metabolites from blood. For this reason measurement of renal clearance is necessary in a clinical practice. Clearance of blood plasma from metabolites takes place in two parts of a nephron, as a result of two different processes; therefore, it is possible to determine clearance values specific for those processes: glomerular filtration rate (GFR), tubular extraction rate (TER) and also

effective renal plasma flow (ERPF) combining both mentioned above renal functions.

Glomerular filtration rate is considered the best measure of renal function among types of clearance specified above, in both healthy and sick people. However, measurement of GFR in clinical practice is troublesome. For this reason renal function is usually assessed from serum creatinine level. In order to make this troublesome measurement of GFR easier, several equations were developed, allowing the assessment of GFR from serum creatinine level, patient age, sex and body size [1–7]. Although in general those equations can be used to assess renal function in clinical practice, one should keep in mind that they were developed after assumption of several simplifications and therefore calculated values may be burdened with a relatively large error. Moreover, serum creatinine level depends not only on filtration rate, but also some other factors

Correspondence to: Prof. Anna Płachcińska MD, PhD
Department of Quality Control and Radiological Protection, Medical University in Łódź, Czechosłowacka 8/10, 92–216 Łódź, Polska, tel.: 605 042 795, e-mail: anna@csk.umed.lodz.pl

like protein consumption [8]. For these reasons, precision and accuracy of GFR assessed from serum creatinine level are poor.

Substances labeled with radionuclides proved to be highly useful in measurements of clearances. They allowed the assessment of renal clearance after a single injection of a radiopharmaceutical, without measurements of activity secreted with urine [9–20].

First methods applied for renal clearance assessments were based on a two-compartment open model of distribution and elimination of endogenous creatinine, developed by Sapirstein et al. [9], which was further adapted for radiopharmaceutical applications [10–14]. Those methods are considered "gold standard" and are still in use. They apply a formula which takes into account activity of administered radiopharmaceutical and also its concentration in blood plasma measured in several [9–12] blood samples taken from 5 minutes to 180 minutes (sometimes even longer) after injection. Those methods are referred to as multi-sample techniques.

In studies aiming at facilitation of measurement of GFR several authors reduced numbers of blood samples. They mostly applied a method named slope/intercept (S/I), which requires two or three blood samples [12–14]. This simplification is with no doubt beneficial, but, on the other hand, authors of those procedures recommend taking blood samples in strictly determined time points after injection. In everyday practice of nuclear medicine departments such requirements not always can be met. Also a long stay in a healthcare facility, sometimes even exceeding 5 hours, can be cumbersome for a patient. Those facts encouraged us to work on a modification of a two-sample method introduced by Russel et al. [15] in order to extend time intervals suitable for blood sampling with possible shortening of patient's stay in a nuclear medicine department. Moreover, introduction of targeted radionuclide therapy into clinical practice, where kidneys are often critical organs and need monitoring [16, 17] increases requirement for relatively simple, quick and reliable method for measurement of renal function.

The aim of the work was to modify a two-sample method used for measurement of GFR, introduced by Russel et al. [15]. This objective was achieved by the following partial goals:

1. Finding a formula variating a parameter of an equation presenting relationship between a reference clearance value and a value calculated from an S/I method.
2. Determination of time intervals suitable for blood sampling providing S/I based clearance calculations close to reference values.
3. Assessment of uncertainty of GFR values calculated with a modified method.

Material and methods

Theoretical basis

GFR calculations are based on a formula derived from a two-compartment open model of a distribution and excretion of a substance:

$$GFR = \frac{A}{\dfrac{A_1}{b_1} + \dfrac{A_2}{b_2}} \tag{1}$$

where: A denotes activity of administered radiopharmaceutical; A_1, b_1, A_2, b_2 are parameters of a function describing a decline of radiopharmaceutical concentration in blood plasma with time.

$$C(t) = A_1 e^{-b_1 t} + A_2 e^{-b_2 t} \tag{2}$$

A first component of the function (2), $A_1 e^{-b_1 t}$, is referred to as a quick phase, because its values decrease rapidly to zero and therefore can be neglected in later parts of a study, typically 60 min after injection. A decrease in a second component, $A_2 e^{-b_2 t}$, is much slower; this is why it is referred to as a slow phase. Calculations of function parameters for a given patient are based on measurements of blood plasma samples taken several times after injection, at early and late stage of a study, fitting of a mathematical formula of a function (2) to measurements; parameters calculated in this way, together with administered activity, can be used in formula (1) for calculation of GFR.

A quick phase vanishes rapidly so a contribution of a low phase to a denominator of formula (1) is by far higher than of the quick one. This is why some authors recommend calculation of renal clearance based on a slow phase only [12–15, 18]. They use the following formula for this purpose:

$$C = \frac{A}{\dfrac{A_2}{b_2}} \tag{3}$$

In order to calculate parameters A_2 and b_2 only two blood samples are necessary, taken in a late phase of a study when contribution of a quick phase is negligible. Cl symbol applies to a clearance value determined with an S/I method from two blood samples.

From a comparison of equations (1) and (3) it is clear that Cl value is larger than GFR, so Cl should be corrected in order to be closer to GFR. Such corrections were proposed by Brøchner-Mortenson [17] and Hagstam et al. [18] who applied a quadratic correction according to an equation:

$$GFR = g \cdot Cl + f \cdot Cl^2 \tag{4}$$

Correction coefficients f and g were determined empirically. So for a first blood sample taken 90 or 120 minutes, and the second one taken 240 minutes after injection, Brøchner-Mortenson [17], Hangston et al. [18] and Tepe et al. [19] calculated the following values for g and f coefficients, respectively: 0.990778 and –0.001218 when GFR was measured in adults and 1.01 and –0.0017 when it concerned children.

However, Russell et al. [15] proposed exponential correction according to an equation:

$$GFR = Cl^\alpha \tag{5}$$

with value of correction parameter $0 < \alpha < 1$, which is also determined empirically. For blood samples taken in $T_1 \approx 60$ min and $T_2 \approx 180$ min the authors obtained $\alpha = 0.979$.

Values of exponent α as well as f and g coefficients may be different for other times of blood sampling because, although a quick phase of a curve is declining fast, it differs between particular time points and its values can affect correction parameters. So, in order to allow for blood sampling in time intervals instead of time points, correction parameters should vary with time.

We applied in our work modification proposed by Russell et al. [15].

The study was approved by the Medical University Bioethics Committee.

Archived data

Archived data of 169 patients who underwent multi-sample studies of GFR measured with ^{99m}Tc-DTPA obtained from kits produced by POLATOM were used. Studies were performed in the Department of Nuclear Medicine of Central Teaching Hospital of Medical University in Łódź. GFR values were included between 5.5 mL/min and 179 mL/min.

An archive of every patient contained GFR values determined with a multi-sample method, coefficients A_1, b_1, A_2 and b_2 of the function (2) describing how a concentration of a radiopharmaceutical in blood plasma was changing with time, as well as count rate [in cpm] obtained from activity A administered to a patient. Using those data, concentrations of a radiopharmaceutical were calculated [in cpm/mL] for every fifth minute between 30 and 190 minutes, which were then treated as measured values.

Paired concentrations C_k, C_l in time points T_k, T_l for $k = 30, 35, 40,...., 120$ and $l = 100, 105, 110, 115,..., 190$, with $l \geq k + 15$ (e.g. C_{30} and C_{100} are concentrations measured from a first blood sample taken in time point $T_{30} = 30$ min and a second blood sample taken in $T_{100} = 100$ min) with time difference $T_l – T_k$ not smaller than 15 min, as well as administered activity were used for calculations of $Cl_{k, l}$. When A_2 and b_2 are calculated from C_k and C_l in samples taken in time points T_k and T_l, respectively, equation (3) after transformation will have the following form:

$$Cl_{k,l} = \frac{A \ln\left(\dfrac{C_k}{C_l}\right)}{T_l - T_k} \exp\left[\frac{T_k \cdot \ln C_l - T_l \cdot \ln C_k}{T_l - T_k}\right] \qquad (6)$$

When $Cl_{k, l}$ values were already calculated for respective GFR values (511 $Cl_{k, l}$ values for every GFR), exponential formula (5) was used to determine a functional relationship between these values. Fitting of equations was based on determination of exponent in such a way that a sum of squares was minimal. Sum of squares of remainders allows determining a standard error of estimate (SEE) of fitting to measured values. These calculations were made using Statistica software.

Selection of time intervals

Time intervals for which a standard error of the estimate (SEE) was not larger than 3.6 mL/min were selected. This criterion is in agreement with a recommendation published by Brøchner-Mortenson [17].

A set of SEE values for which the above criterion is met was used to create a formula presenting relationship between SEE and selected values of T_1 and T_2 (time points of first and second blood sampling, respectively) — SEE (T_1, T_2). This function had a form of a polynomial of a degree for which a coefficient of determination was not lower than 0.996.

Assessment of uncertainty of modified GFR measurement

Uncertainty ΔGFR of modified GFR measurements was estimated using law of error superposition, taking into account prediction error S_{pr}, determined by SEE (see Appendix) and errors made during study performance resulting from uncertainties of blood sampling times ΔGFR_{T1} and ΔGFR_{T2}, pipetting ΔGFR_p and a stochasticity of radioactive decay ΔGFR_s, so:

$$\Delta GFR = \sqrt{(S_{pr})^2 + (\Delta GFR_p)^2 + (\Delta GFR_{T_1})^2 + (\Delta GFR_{T_2})^2 + (\Delta GFR_s)^2}$$

Uncertainties $\Delta GFR_{T1\backslash2}$, ΔGFR_p and ΔGFR_s were assessed from differential of formula (6) taking into account also formula (3), assuming that time measurements errors did not exceed 10 s, pipetting error was equal to 2%, and uncertainty of radioactive sample measurement was not greater than 1%. Own experience of the authors of this work points out that uncertainties of those measurements are smaller in practice. However, it is better to overestimate potential errors than to neglect them.

Results

Figure1 presents an illustrative relationship between $Cl_{60, 125}$ (obtained for times of blood sampling $T_1 = 60$ min and $T_2 = 125$ min) and GFR values together with a fitted curve. A criterion SEE ≤ 3.6 mL/min resulted in selection of the following time intervals: for T_1 between 60 min and 90 min and for T_2 between 150 min and 190 min. Figure 2 illustrates how SEE changes with
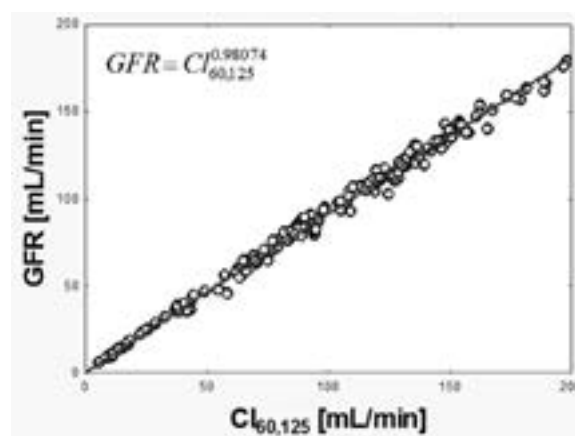

Figure 1. GFR and Cl values obtained for blood samples taken in two time points: $T_1 = 60$ min and $T_2 = 125$ min together with a curve presenting a relation between those variables. $R^2 = 0.98074$, SEE = 3.37 mL/min
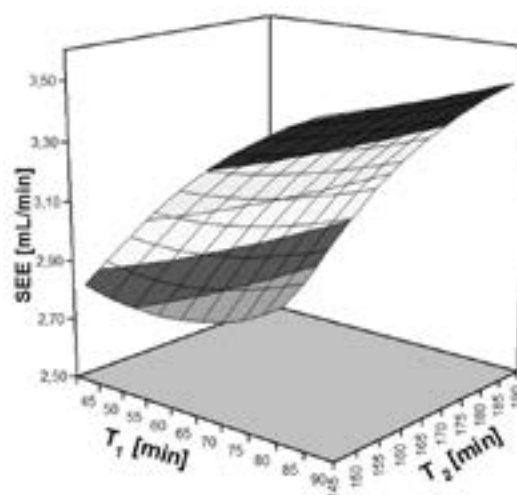

Figure 2. Relation between SEE and time points of first (T_1) and second (T_2) blood sampling

Table 1. SEE values [mL/min] determined for ends of time intervals

T_2	T_1	
	60 min	90 min
150 min	3.08	3.5
180 min	2.91	3.47

Table 2. Values of α exponents determined for ends of time intervals

T_2	T_1	
	60 min	90 min
150 min	0.98162	0.98052
180 min	0.98228	0.98068

time of blood sampling and in Table 1 its values for ends of time intervals are presented. For other pairs of blood sampling times, values of SEE will be intermediate.

A relation between SEE and blood sampling times T_1 and T_2 is characterized by an experimentally derived polynomial function (see: Selection of time intervals):

$$\begin{aligned} SEE(T_1,T_2) = &(-1.017\cdot10^{-9}T_2^2 + 3.351\cdot10^{-7}T_2 - 2.792\cdot10^{-5})\cdot T_1^3 + \\ &+ (2.66\cdot10^{-7}T_2^2 - 8.9606\cdot10^{-5}T_2 + 0.007383)\cdot T_1^2 + \\ &+ (-2.4\cdot10^{-5}T_2^2 + 0.008502T_2 - 0.6902)\cdot T_1 + \\ &+ (0.000804\cdot T_2^2 - 0.2893T_2 + 26.703) \end{aligned} \quad (7)$$

In Table 2 values of exponent α calculated for ends of time intervals are presented. It can be seen that a difference between maximal and minimal values of this exponent does not exceed 0.0017. This is why a constant value of exponent α equal to its mean value of 0.9812 was accepted instead of varying it with sampling times.

SEE values given in Table 1 and calculated from formula (7) make up the smallest width of so called error corridor (referred to as prediction error) achieved for mean abscissa and ordinate values. For minimal and maximal values of GFR a width of an error corridor (prediction error) increases only by 0.1%, which equals to 0.0003 mL/min. For this reason a constant prediction error for a whole range of calculated clearence values equal to SEE was accepted while assessing the uncertainty of modified calculations of GFR results.

Figure 3 illustrates how uncertainty of GFR measurement changes with its value, when blood sampling is made in 90 minute and 150 minute after injection. It can be seen that a whole uncertainty is determined mostly by the prediction error and pipetting error and to a much lesser extent by timing errors.

Figure 4 presents how a whole relative uncertainty (precision) of GFR measurement changes, when blood sampling is made at least (90 and 150 minutes) and most (60 and 180) appropriate times after injection. Differences between those values are considerable for low GFR values — from 5 mL/min to 15 mL/min and are equal to 11% and 6%, respectively. Then, above 15 mL/min these differences in precision decline to 2.5% for GFR $\approx$20 mL/min, to 2% for GFR $\approx$30 mL/min, to 1.5% for GFR $\approx$45 mL/min and to 0.25% for GFR $\approx$180 mL/min. It corresponds to differences in absolute uncertainties at least and most appropriate measurement conditions from about 1 mL/min to 0.5 mL/min. For other T_1, T_2 pairs taken from earlier selected time intervals the whole uncertainties are comparable and do not exceed mentioned above values.
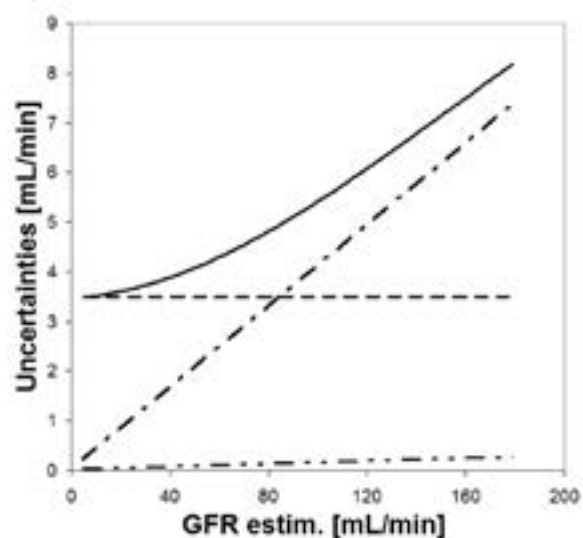
Figure 3. Relation between total uncertainty of measurement (solid line) and its components: prediction error (dashed line), pipetting uncertainty (dotted line), time uncertainty (double dotted line) and measured GFR values when blood samples are taken 90 and 150 minutes after injection
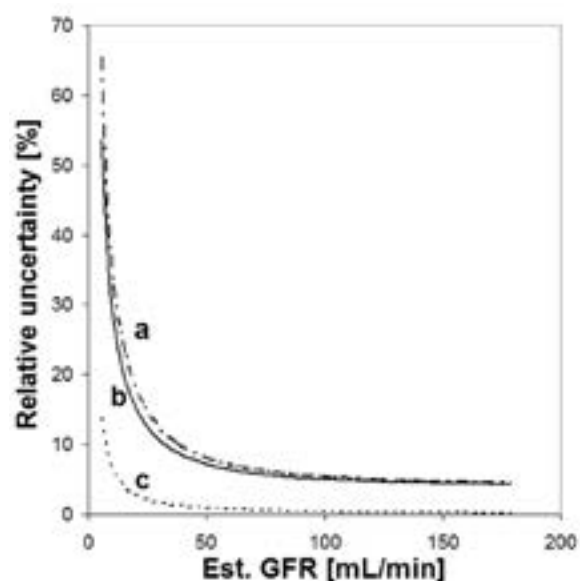
Figure 4. Relative total uncertainty of GFR measurement in relation to its values for blood samples taken 90 and 150 minutes after injection (a), 60 and 180 minutes after injection (b). Line (c) presents a difference between (a) and (b)

Discussion

Brøchner-Mortensen as well as other authors proved that it is possible to measure GFR after taking only two blood samples 3–5 hours after injection of ^{51}Cr-EDTA or ^{99m}Tc-DTPA [15, 18–20]. Analyses presented in this work confirm this possibility, also when blood samples are taken in other time points than those recommended by the authors mentioned above, preserving equal value of a standard error of estimate (SEE), namely 3.6 mL/min,

as recommended by Brøchner-Mortensen et al. [17]. This criterion is met when a first blood sample is taken in time 60 min ≤ T_1 ≤ 90 min, and the second one at 150 min ≤ T_2 ≤ 180 minutes after injection.

Calculated values of exponent α vary from 0.98052 for a shortest time interval between blood samplings (T_1 = 90 min, T_2 = 150 min) to 0.98228 for blood samples taken 60 and 180 minutes after injection. Those values, although slightly higher, are in good agreement with a value 0.979 presented in a publication by Russel et al. [15].

Minor, smaller than 0.2%, variability of exponent α in determined time intervals allows using its mean value, namely 0.9812, for time pairs T_1, T_2 instead of calculating its exact value. Chantler et al. [11] proceed in the same way, even when blood samples are taken in times points different from those recommended by Russell et al. [15]. However, a mean value used instead of a calculated one for a given time pair T_1 and T_2 changes accuracy of a resultant value, especially when blood samples are taken at ends of time intervals. Our analysis proved that accuracy of calculated values in case of most unfavorable times T_1 and T_2 will not exceed 1 mL/min when GFR ≈ 180 mL/min. This inaccuracy decreases with decline of GFR values and reaches 0.02 mL/min for GFR ≈ 10 mL/min. Such a small change of accuracy does not affect interpretation of calculated GFR values. On this basis the modified method for GFR calculation may be considered sufficiently accurate.

In every method used for measurement of a given quantity an uncertainty of its results should be also assessed. This task was also performed in this work. As mentioned earlier, a model of a relation between modified and full measurement of GFR, referred to as a prediction error determined by SEE, as well as manual activities contribute to uncertainty of results.

Obtained results point out that a prediction error determined by SEE for optimal time points of blood sampling is equal 2.9 mL/min and for less favorable times it reaches 3.5 mL/min for middle values of GFR. Moreover, for extremely low and high GFR values, 10 mL/min and 180 mL/min, respectively, a prediction error increases only by 0.001 mL/min, for optimal as well less favorable times of blood sampling. For this reason a prediction error can be considered constant for the whole range of analyzed GFR values, its value depending only on blood sampling times. This error cannot be completely eliminated, only minimized. This is why possibly long time laps between blood samplings are recommended.

Manual activities are another source of a significant error. Analysis of uncertainties revealed a relatively high contribution of pipetting in this error. This contribution grows with GFR value and for high clearance values it surpasses a prediction error. Relations presented in Figure 4 were calculated for 2% pipetting precision, which is a realistic value of this kind of error.

As can be seen in Figure 3, errors in time measurements affect overall uncertainty of measurements to a lesser extent. Accepted uncertainty of time measurement was 10 seconds, an excessive value for vast majority of cases.

After considering all partial uncertainties and adding them according to a law of error superposition a relation between total absolute uncertainty of GFR measurement and its value was obtained (Fig. 3). As can be seen, uncertainty of absolute measurement increases with its value, from about 4 mL/min for GFR equal to 5–10 mL/min to about 8 mL/min for GFR = 180 mL/min, when blood samples are taken 90 and 150 minutes after injection. When blood sampling is made at more favorable time points, like 60 minutes and 180 minutes after injection, a curve presenting uncertainty of measurement is located about 0.5 mL/min lower. So, for time intervals selected earlier uncertainties of measurement are almost equal.

Precision is a metrological characteristic of a measurement procedure. In this case a relative measurement uncertainty may be accepted as a measurement precision. Figure 4 presents its relation to GFR values for optimal and most unfavorable time points of blood sampling. When samples are taken at optimal time points (60 and 180 minutes), a relative uncertainty of measurement falls abruptly from 55% for GFR = 5 mL/min to 10% for GFR = 30 mL/min and then mildly to about 5% for GFR = 180 mL/min (Fig. 4, solid line). When blood samples are taken at least favorable time points (90 and 150 minutes) a shape of a curve is similar but its values are higher by about 10%. For higher GFR values differences between uncertainties decrease and for GFR = 180 mL/min both curves overlap. All in all, a precision of GFR measurement with a modified method is satisfactory for blood sampling at all time points within earlier determined time intervals. Moreover, for GFR > 40 mL/min a measurement precision is comparable with precision of a multi-sample method [21].

It should be also mentioned that results of GFR measurement, in order to be comparable among patients, should be normalized to patient body surface, which can be calculated from the Haycock [22] formula:

$$BS = 0.024265 \cdot H^{0.3964} M^{0.5378}$$

where BS — body surface in m², H — patient height in cm, M — body mass in kg.

Conclusions

1. Time intervals selected for blood sampling, 60 to 90 minutes for the first and 150 to 180 for the second one, fully satisfy nuclear medicine staff. Three-hour study duration is acceptable for patients.
2. Uncertainties of measurements when blood samples are taken in specified above time intervals are low, and for high GFR values even comparable with uncertainties of multi-sample method.
3. The proposed modification of GFR measurement method provides credible results.
4. A software applying formulae used in this method can be coded easily and applied in practice.

Appendix

In statistics a mean squared prediction error S_{pr} of a smoothing or curve fitting procedure is the expected value of the squared difference between the fitted values and the values of the smoothed function.

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