Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
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Citation for published version (APA):
Kemperman, F. A. W. (2001). Improvements in the use of plasma creatine as a marker of the glomerular filtration rate

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Appendix

Refining the method for measurement of the glomerular filtration rate using correction for inaccurate urine collections and for varying plasma tracer concentrations.

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Appendix

Abstract

Measurement of the glomerular filtration rate (GFR) is important for assessment of the severity of renal disease or renal involvement of systemic disease. The reference method for measurement of the GFR is the bladder clearance of continuously infused inulin, as described by Homer Smith. However, bladder catheterization and continuous infusion are inconvenient for patients and the determination of inulin is cumbersome. Therefore, several other methods for measurement of the GFR have been developed and the pro's and con's have been described in this article. These methods can be divided in urinary clearance and plasma clearance methods after either continuous infusion, intravenous bolus injection or subcutaneous administration of inulin, radioactive tracers or iodinated contrast agents. Plasma clearance methods have the disadvantage of extrarenal clearance, intravenous bolus injections are hampered by the difficulty of obtaining equilibrium between plasma and interstitial fluid. After subcutaneous administration stable plasma concentrations will not be reached in all patients. Even during continuous infusion of a tracer stable plasma concentrations are not reached, because of the circadian rhythm of GFR. This review analyzes the weak points of the various GFR methods and describes a method using correction for inaccurate urine collection and for varying plasma concentrations, that can be applied in clinical practice.
Introduction

Assessment of the glomerular filtration rate (GFR) is important for clinical management and therapeutic trials in patients with renal diseases. Most often an approximation of the GFR is obtained using the endogenous creatinine clearance, either measured in a timed urine sample or assessed by a formula or nomogram incorporating plasma creatinine. However, GFR is overestimated by the creatinine clearance due to tubular secretion of creatinine, especially in patients with proteinuric glomerular disorders [1,2].

The ideal marker to measure GFR should meet the following criteria: it is a low molecular weight solute, unbound to plasma proteins and thus freely filterable in the glomerulus; it is neither secreted nor reabsorbed by the tubules and neither stored, synthesized nor metabolized by the kidney; it is inert, non-toxic and does not affect renal function; it yields a constant clearance over a wide range of plasma concentrations, and plasma and urine concentrations can be determined accurately [3-5]. Inulin is a fructose polymer derived from natural sources, with an approximate molecular weight (MW) of 5200 Dalton (D). It meets all criteria, only trace amounts may be secreted into the bile [3]. However, accurate measurement in the laboratory is cumbersome. Therefore, several other substances for GFR-determination have been developed: radioactive tracers such as $^{51}$Cr-EDTA (MW 292 D), $^{125}$I-iothalamate (614 D) and $^{99m}$Tc-DTPA (393 D, with a short isotopic half-life of only 6 hours). The use of iodinated contrast agents such as diatrizoate and iohexol has also been described [6,7].

Measurement of GFR with these markers is not without technical problems. First, inadequate urine collections obtained by spontaneous voiding will lead to an inaccurate GFR-calculation, when a renal clearance is measured. Second, when a plasma clearance is calculated, GFR will be overestimated due to the extrarenal clearance of the tracer. Third, it takes time for the tracer to penetrate the whole volume of distribution, before a steady state plasma concentration can be obtained. This is in part dependent on the molecular weight of the tracer. And fourth, it should be realized that during continuous infusion of a tracer a steady state can not be reached, because of the circadian rhythm of GFR.
Administration of the tracer and clearance measurement

One way to administer a tracer is by continuous infusion. The renal or urinary clearance of continuously infused inulin after an oral water load, described by Homer Smith and generally accepted as the reference method for GFR-measurement, is calculated with the formula

\[ \frac{U \cdot V}{P} \]  

(Formula 1, Standard Method or StM)

where U = the inulin concentration in urine, V = the urine flow rate per unit time, determined by bladder catheterization and P = the inulin concentration in plasma [8]. The urinary clearance of the radiotracer \(^{125}\)I-iothalamate, administered by continous infusion, is in close agreement with that of inulin [9].

Because accurate urine collections are sometimes difficult to obtain without bladder catheterization, the infusion-equilibrium technique has been developed by Earle and Berliner [10]. This technique is based on the assumption that in a steady state of plasma tracer concentration the amount of infused tracer \((I \cdot V)\) is equal to the amount of excreted tracer \((U \cdot V)\), where I = infusate concentration and V = infusion rate. The product \(I \cdot V\) can replace \(U \cdot V\) to obtain the plasma or infusate clearance of a continuously infused tracer:

\[ \frac{I \cdot V}{P} \]  

(Formula 2, Constant Infusion Method or CIM)

Berger et al. reported good agreement between CIM and StM in normal subjects in the absence of edema [11]. However, the CIM or infusate clearance is less accurate than the StM or urinary clearance because of difficulties to obtain constant plasma tracer concentrations [12], slow penetration into the less permeable components of the extracellular fluid compartment [13], and some extrarenal clearance of tracers. The CIM-clearance of \(^{125}\)I-iothalamate overestimated the StM-clearance by 5 ml/min in 40 renal patients with a StM-clearance ranging from 12 to 140 ml/min, especially in the low range [14]. In 25 renal patients the mean CIM-clearance of inulin was 53.8 ml/min/1.73m\(^2\) and the mean StM-clearance 48.3 ml/min/1.73m\(^2\); the overestimation ranged from 0 to 10 ml/min/1.73m\(^2\) and was similar over the whole GFR-range [15].
Another way of tracer administration is by single shot intravenous bolus injection. It was first introduced by Alving and Miller and avoided the inconvenience of continuous infusion [16]. The plasma decay curve showed two exponential components: the first rapid decrease represented inulin movement into the interstitial space, the second slower decrease represented loss from the entire extracellular space by glomerular filtration [17]. Both urinary and plasma clearance techniques have been developed using bolus injections of inulin, $^{51}$Cr-EDTA or $^{99m}$Tc-DTPA [3,18,19].

From a single intravenous injection the urinary clearance has been measured. The drawbacks of this approach have been summarized by Homer Smith [3]: (1) true equilibrium between plasma and interstitial fluid occurs at only one moment after injection; (2) tracer concentrations in peripheral venous blood are higher than those in mixed venous blood and therefore also in renal arterial blood, because the mixed venous blood is diluted by the renal venous blood. The too high peripheral venous blood concentration falsely lowers the clearance measurement; (3) the transit time of urine from kidney to bladder makes it difficult to choose an appropriate midpoint plasma tracer concentration from a falling curve. According to Perrone et al. the urinary clearance of $^{99m}$Tc-DTPA after a single shot overestimated GFR, measured by the StM inulin clearance, by approximately 10% in normal subjects [20].

After a single intravenous bolus injection the plasma clearance has also been calculated from one or more plasma samples, drawn during the second part of the plasma decay curve. This method has been used in studies on progression of diabetic nephropathy in Europe [21,22]. However, the decay curve is not only caused by renal clearance, but also by extrarenal clearance and by penetration of tracer into the whole volume of distribution. Consequently, the plasma clearance overestimates the urinary clearance after a bolus injection of $^{99m}$Tc-DTPA, $^{51}$Cr-EDTA or inulin by 6 to 8 ml/min in patients with renal impairment [23], and even more in patients without renal impairment [24].

Another way to administer a tracer is by a single subcutaneous injection. This technique has been developed for measurement of the urinary clearance of $^{125}$I-iothalamate. It was administered either with epinephrine in the deltoid area to ensure slow release from the subcutaneous tissue or without epinephrine [25,26] A stable plasma $^{125}$I-iothalamate concentration was observed in all patients with administration of epinephrine, whereas a decrease was seen in patients without epinephrine and normal or mildly impaired renal function. Despite this, the $^{125}$I-iothalamate clearance correlated well with the StM inulin clearance. Urine samples were obtained by
spontaneous voiding. The method without administration of epinephrine has been used in clinical trials in the United States of America [27,28].

The day-to-day variability of a GFR-measurement is important, when GFR is used for follow-up of a renal disease or after an intervention. For example, the coefficient of variation (CV) of GFR, measured as the urinary clearance of subcutaneously administered $^{125}$I-iothalamate, has been reported to be 6.3-16.6 % [20,27,28]. This is high, because the critical difference between two measurements is $2\sqrt{1+(CV_1)^2+(CV_2)^2}$ or 18.47 % [29]. The accuracy and precision of the GFR, measured by the urinary clearance of a continuously infused tracer, can be improved using two corrections: (1) a correction for inaccurate urine collections during the clearance studies, in case no bladder catheterization is performed and (2) a correction for a changing plasma tracer concentration. In the next two paragraphs we will describe these corrections in detail.

**Correction for inaccurate urine collections**

A method to correct for inaccurate urine collections has been described by Donker et al. [14]. They studied 72 patients who were able to collect their urine satisfactorily without catheterization. The clearance of $^{125}$I-iothalamate (IOT) during continuous infusion was used for measurement of GFR and that of $^{131}$I-hippuran (IOH) for the effective renal plasma flow. The clearance was calculated as the mean value of two 2-hour clearance periods after 2 hours of equilibration. Two-hour urine collection periods minimize the problem of ‘dead space’, due to the transit time of urine from the kidneys to the bladder. It was found that the *infusate* clearance of IOH ($I^{*}V/P$ or ClM) was equal to the *urinary* clearance ($U^{*}V/P$ or StM), in 40 patients with an IOH clearance above 100 ml/min. This was most likely caused by rapid movement of IOH into its volume of distribution, the presence of stable plasma concentrations after 2 hours of continuous infusion and the absence of extrarenal clearance. Therefore, errors in urine collection could be corrected by dividing the *infusate* clearance ($I^{*}V/P$) of IOH by the *urinary* clearance ($U^{*}V/P$) of IOH, or simplified by:

$$\frac{I_{IOH}^{*}V_1}{U_{IOH}^{*}V_U}$$

(Formula 3, Urine Correction Factor)
Refinement of GFR-measurement

where \( I_{\text{IOH}} \) = the concentration of IOH in the infusate or counts per minute per ml of infusate, \( V_i \) = the infusion rate, \( U_{\text{IOH}} \) = the concentration of IOH in urine or counts per minute per ml of urine and \( V_u \) = the urine flow rate during a clearance period. The infusate clearance of IOT was higher than the urinary clearance, probably due to extrarenal clearance and/or slow distribution. The urine correction factor can be multiplied with the urinary clearance of IOT (\( U^*V/P \)) to obtain a GFR-measurement that is free from urine collection errors and extrarenal clearance. We studied 24 renal transplant patients performing 48 two-hour clearance periods. In one-third of these periods the inaccuracy in urine collection was more than 10 % (unpublished data).

Repeated measurements of the GFR using this urine correction method showed a day-to-day variability of only 2.2 % in 28 patients with an IOH clearance of 200 to 600 ml/min [14]. This has important implications for the follow-up of GFR. Since the coefficient of variation is 2.2 %, the critical difference between two GFR-measurements is only 6 %, much better than the abovementioned value of 18-47% observed when correction for inaccurate urine collections was not used. In a study on long-term slope calculations of GFR-changes, using the same clearance techniques as Donker et al., the intratest coefficient of variation between two clearance periods was found to be 1.9 % for the urine correction method and 8.5 % for the standard method [30]. The intertest coefficient of variation between two GFR-measurements was 2.9 % for the urine correction method and 5.1 % without this correction. Consequently, the precision of the GFR-slope was significantly better with the urine correction method compared to the standard method. This is important for both individual patients and for study purposes. The urine correction method reduced the necessary sample size needed to detect a GFR-slope difference between interventions with 70 % [30].

Correction for varying plasma tracer concentrations

The plasma tracer concentration is often regarded as stable during continuous infusion, but this is not correct [12,15]. The tracer infusion rate is estimated from the endogenous creatinine clearance, either measured or assessed by a formula based on age, gender, body weight and plasma creatinine concentration [31]. Incorrect estimations of the real GFR will lead to a gradual increase or decrease of the tracer concentration during continuous infusion. Even when the infusion rate is correct, plasma concentrations will fluctuate due to the circadian rhythm of GFR, which has a mean day-night difference of 20 to 33 % both in normal individuals and in patients with nephrotic syndrome [2,17,32,33]. The maximum GFR is usually reached between noon and
4 P.M., but the time of maximum GFR varies between individuals. The effective renal plasma flow has a circadian rhythm with a mean day-night difference of 25 to 35 %, and a maximum value between 2.30 and 8 P.M. This leads to a systematic trend of the plasma tracer concentrations, downward before noon and upward in the evening.

An increase in plasma tracer concentration indicates that part of the infused tracer accumulates in the volume of distribution and thus in blood, rather than in the urine. As a consequence, the CIM \textit{infusate} clearance is higher than the real GFR [15,32]. Conversely, a decrease will cause a lower CIM clearance, compared to the real GFR. Consequently, a correction is necessary for increasing or decreasing plasma tracer concentrations. For IOH the \textit{infusate} clearance, which equals the \textit{urinary} clearance, is calculated as $I^V/P$. The amount of increased or decreased body tracer content can be calculated by the plasma concentration difference multiplied with the volume of distribution (Vd) of the tracer. This amount should be subtracted or added to $I^V$. This gives a new equation:

$$I^V + (P_0 - P_e) \times V_d$$

Where $P_0 = the$ plasma tracer concentration at the beginning of a clearance period, $P_e = the$ plasma tracer concentration at the end of a clearance period, and $P = the$ arithmetic mean of $P_0$ and $P_e$; Vd for IOH is the extracellular volume or 25 % of the body weight [31]. We compared the IOH clearance with and without the correction for changing plasma tracer concentrations in 24 renal transplant patients. The median difference between the two was 5 % and in six of the patients it was more than 10 %, up to 35 % difference (unpublished data).

From the Modified CIM the \textit{urinary} clearance of IOT can be calculated using a modification of the correction factor for inaccuracies in urine collection:

$$\frac{I^V \times V_f + (P_0 - P_e) \times V_d}{U_{IOH} \times V_U}$$

(Formula 5, Modified Correction Factor)

This factor has to be multiplied with the \textit{urinary} clearance of IOT to obtain a GFR-measurement that lacks errors for urine collection, extrarenal clearance, and changing plasma tracer concentrations. Using all corrections described above a GFR formula can be composed:
Refinement of GFR-measurement

\[
\text{GFR} = \frac{\text{Modified } C1M_{IOT}}{\text{StM}_{IOT} \ast \text{StM}_{IOT}} \quad \text{or} \quad \frac{I_{IOT}^{V1} + (P_o - P_e)^{Vd}}{P_{IOT}} = \frac{U_{IOT}^{Vd} \ast V_u}{P_{IOT}} 
\]

GFR = \frac{I_{IOT}^{V1} + (P_o - P_e)^{Vd}}{U_{IOT}^{Vd} \ast V_u} \quad \text{or} \quad \frac{U_{IOT}^{Vd} \ast V_u}{P_{IOT}} \quad (\text{Formula 6, Urinary IOT-clearance after correction for inaccurate urine collections and for varying plasma tracer concentrations})

Conclusions

The various ways of GFR-measurement using different tracers and techniques have been discussed. The pro’s and con’s of these methods have been described: methods are either accurate but laborious and time consuming or less laborious but also less accurate. It follows from the discussed evidence that an accurate and clinically achievable method for the measurement of GFR without bladder catheterization is obtained using the urinary clearance of continuously infused $^{125}$I-iothalamate, provided that $^{131}$I-hippuran is administered simultaneously. This allows the necessary correction for inadequate urine collections and for changing plasma concentrations. The method can be used for clinical purposes and for intervention studies, reducing the number of patients to treat for the detection of a change in GFR-slope.

Acknowledgements

We thank Dr. B.A.C. van Acker and Professor Dr. A.J.M. Donker for their critical review of this manuscript.
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