Kinetic Glomerular Filtration Rate in Routine Clinical Practice—Applications and Possibilities

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When the [creatinine] is changing, the kidney function can still be tracked with a quantitative technique called kinetic glomerular filtration rate (GFR). The equation yields useful information on the severity of acute kidney injury, the clinical course of kidney and dialysis clearances, and the timing of kidney recovery. It has been validated in at least 3 independent studies, where it performed sufficiently well in intensive care unit and kidney transplant settings, and in head-to-head comparisons with biomarkers. Because it is based on a mathematical model, the kinetic GFR faces limitations depending on the accuracy of its assumptions. As the assumptions more accurately reflect the complexities of biology, some of these limitations can be overcome in a more sophisticated model. Kinetic GFR is an easy-to-use, low-cost tool that should be more widely incorporated into medical practice.

Key Words: Creatinine, Clearance, Equation, Biomarker, Cystatin C

INTRODUCTION

Nephrologists are asked to consult on acute kidney injury (AKI) in the hospital on an almost daily basis. AKI is evaluated by tracking the underlying kidney function. If the glomerular filtration rate (GFR) has plummeted, the AKI is judged severe and that raises a set of differential diagnoses, likely to include acute tubular necrosis (ATN).[1] If the GFR is merely drifting downward, the AKI is milder and that triggers another set of differential diagnoses, usually based on hemodynamic effects.[2] The kidney function is typically seen through the lens of the serum creatinine (S_{Cr}), a picture that can be obscure at times. The distortion comes from the fact that S_{Cr} lags behind the kidney function.[3] The GFR may drive the changes in S_{Cr}, but it can take several days for the S_{Cr} to reach a new steady-state and catch up to the underlying GFR.[4] If the creatinine lag can be converted into information on GFR without waiting for steady-state, the advance knowledge will help doctors make sound decisions more quickly.[3]

The purpose of the kinetic GFR is to estimate the kidney function even while the creatinine is "in motion," that is, changing acutely. Physicians do a qualitative version of this, for example, when they see the S_{Cr} rise by more than 1 mg/dL in a day. We are taught that the rapid rate of rise indicates a severe impairment in the kidney function, often due to ATN, and that the GFR should be assumed to be <10 mL/min.[5] For slower rates of creatinine rise, we scale back the kidney impairment and maybe surmise that the GFR lies between 10 and 40 mL/min. Can we be more quantitative than that? The kinetic GFR was developed for this reason.

METHODOLOGY

Let us model the kidney clearance of creatinine with a thought experiment. Shrink the body so that the entire serum volume fits into just 10 dL (Fig. 1). To start off with a normal S_{Cr}, those 10 dL would contain 10 mg of creatinine for a [Cr] = 1 mg/dL. If the muscles produce 10 mg of creatinine per cycle, an arbitrary unit of time for computational purposes, then the kidneys would have to excrete 10 mg of creatinine in the same cycle to keep the serum [Cr] stable at 1 mg/dL. The matched input and output of creatinine leads to a dynamic equilibrium, known as a steady-state. The 10 mg of creatinine that was excreted came from 10 dL of serum, and since that volume was completely cleared of its creatinine content, the kidney clearance or GFR is 10 dL per cycle.

Now let us break steady-state by inducing ATN. The GFR suddenly drops by 90%, from a clearance of 10 to 1 dL per cycle. What happens in the next cycle (Fig. 2)? Currently, each 1 dL contains 1 mg of creatinine, so the acutely injured kidney can only excrete 1 mg of creatinine. In the meantime, the noninjured muscles continue to produce 10 mg of creatinine. That leads to a net positive balance of $10-1 = 9$ mg of creatinine. These 9 mg are added to the serum that started off with 10 mg of creatinine, bringing the new total up to 19 mg (Fig. 2). The serum volume is still 10 dL, so the new $[Cr] = 19/10 = 1.9$ mg/dL. The S_{Cr} has risen from 1.0 to 1.9 mg/dL in one cycle.

If ATN persists and the GFR remains at 10% of normal, the next cycle yields the following (Fig. 2). On the output side, each 1 dL now contains 1.9 mg of creatinine. The reduced GFR of 1 dL per cycle means that the kidneys excrete 1.9 mg of creatinine. As before, the muscles continue to produce 10 mg of creatinine in a cycle. That leads to a net positive balance of $10-1.9 = 8.1$ mg. When the 8.1 mg is added to the prior creatinine total of 19 mg, the serum contains 27.1 mg of creatinine, and the new S_{Cr} is $[Cr] = 27.1/10 = 2.71$ mg/dL (Fig. 2). The next cycle would yield a kidney excretion of 2.71 mg creatinine, a net positive balance of 7.29 mg, and a new S_{Cr} of 3.44 mg/dL.

A S_{Cr} rising from 1.0 to 1.9 to 2.71 to 3.44 mg/dL realistically recreates the clinical course of ATN. The S_{Cr} goes up rapidly at first, but then, the trajectory slows down on its way to reaching a plateau. The steady-state S_{Cr} is dictated by the underlying GFR, and our small-scale

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experiment mimics that reality. When the S_{Cr} reaches 10 mg/dL, each 1 dL of serum contains 10 mg of creatinine. The GFR may still be impaired at 1 dL per cycle, but the kidneys are now able to excrete 10 mg of creatinine, matching the muscle creatinine production and achieving a new steady-state of $[Cr] = 10$ mg/dL. Paradoxically, the efficiency of kidney creatinine excretion improves during AKI.

In our hypothetical experiment, we were told the change in GFR (90% loss) that was going to drive the evolution of S_{Cr}. The math permits calculation of subsequent creatinines (1.0 to 1.9 to 2.71 to … mg/dL). But in the real world, we are told the patient's [creatinine]s by the laboratory, and we have to work backward to deduce the underlying GFR.[3] The math is more complicated because we have to calculate the GFR it would have taken to get from creatinine "A" to creatinine "B" in "x" amount of time.

HISTORY

Essentially, the task of working backward through the math is what the kinetic GFR equation is accomplishing. Historically, several groups had previously formulated versions of kinetic GFR. They are all based on the first principle that the change in body creatinine equals the amount coming in minus the amount going out. The latter creatinine excretion can be expressed in terms of GFR. Incorporating time turns the principle into a related-rates problem, and the resulting equation predicts the target S_{Cr}. Some of these equations can be rearranged to solve for GFR.

CLINICAL SUMMARY

- When the [creatinine] is changing, the kidney function can still be ascertained by the kinetic glomerular filtration rate (GFR) equation.
- Tracking the kinetic GFR yields useful and actionable information for patient care.
- Viewed as a kinetic GFR graph, the clinical course of acute kidney injury or kidney recovery is clarified.
- The simplified mathematical model can be enhanced to accommodate a changing body volume.

The first kinetic formula was done in 1972 by Jelliffe and Jelliffe[6,7] and later revised in 2002. The derivation used empiric values and said that $10 \cdot 0.4\ W \cdot \Delta[Cr]/\Delta t = Gen - 1,440\ KeGFR \cdot [Cr]_{Mean}$, where W is the body weight, 0.4 is the fraction that is the volume of distribution (V_d) for creatinine, $\Delta[Cr]/\Delta t$ is the rate of change in S_{Cr} per day, Gen is the creatinine generation rate (mg/d), and 1440 is the number of min/d. $[Cr]_{Mean}$ is the average of 2 [creatinine]s. Then, $KeGFR$ has units of dL/min that can be multiplied by 100 to be in mL/min. Basically, it restates the first principle that the rate of change in body creatinine, $V_d \cdot \Delta[Cr]/\Delta t$, equals the generation rate, Gen, minus the excretion rate, 1440 $KeGFR \cdot [Cr]_{Mean}$.

The next kinetic formula was done in 1975 by Chiou and Hsu.[8] Their formula said that

$$[Cr]_{(t)} = \left[Gen - (Gen - KeGFR \cdot [Cr]_0) \cdot e^{-\frac{KeGFR}{V_0} t} \right] \Big/ KeGFR,$$

where $[Cr]_{(t)}$ is the S_{Cr} at time t, and V_0 is the creatinine volume of distribution. e is the base of the natural logarithm and is ~2.7183. Since $KeGFR$ appears 3 times on the right-hand side, the equation is not an explicit solution for kinetic GFR.

The next kinetic formula was in 1985 by Moran and Myers.[2] It said that $KeGFR = \left(Gen - \frac{d[Cr]}{dt} \cdot V_0 \right) \Big/ [Cr]_{(t)}$. The equation is the first to explicitly solve for kinetic GFR, but it contains a derivative of creatinine with respect to time, an instantaneous rate that is not always easy to determine in practice.

The next equation was in 2012 by Yashiro and colleagues.[9] It states that $KeGFR = \left(Gen - \frac{\Delta[Cr]}{\Delta t} \cdot V_0 \right) \Big/ [Cr]_{Mean}$ and approximates the equation of Moran and Myers. Instead of using a derivative for the instantaneous rate of change in S_{Cr}, Yashiro's equation uses the average rate of change, $\Delta[Cr]/\Delta t$. As such, it divides by the average creatinine, $[Cr]_{Mean}$, rather than the instantaneous creatinine, $[Cr]_{(t)}$.

METHODOLOGY REDUX

The above equations share much in common but are not necessarily user friendly. Thus, I developed a noncalculus, algebraic version of the kinetic GFR in 2013. The relevant clinical data are (1) how fast the S_{Cr} changes: $\Delta[Cr]/\Delta t$ (note: $\Delta[Cr]$ is negative in sign if $[Cr]$ is decreasing), (2) the fastest that the S_{Cr} could increase, in theory, per day (as if anephric; value is ~2.5 mg/dL per day): $\Delta[Cr]/\Delta t|_{Max}$, (3) the average of the 2 consecutive creatinines: $[Cr]_{Mean}$, (4) a S_{Cr} at steady-state: $[Cr]_{SS}$ (eg, the baseline S_{Cr} just prior to an episode of AKI), and (5) the estimated GFR corresponding to that steady-state S_{Cr}: $eGFR_{SS}$. The 5 variables are manipulated to yield the kinetic GFR in the equation: $KeGFR = eGFR_{SS} \cdot [Cr]_{SS}/[Cr]_{Mean} \cdot \left(1 - 24 \frac{\Delta[Cr]}{\Delta t} / \frac{\Delta[Cr]}{\Delta t}\Big|_{Max} \right)$.[3]

By configuring the math so that it conforms to the way that physicians practice, I hoped to create a practical tool that could be deployed at the bedside.

The first half of the equation, $eGFR_{SS} \cdot [Cr]_{SS}/[Cr]_{Mean}$, is analogous to the "static" clearance equation, $CrCl = U_{[Cr]} \times V_{Urine\ Rate}/S_{[Cr]}$. In place of $U_{[Cr]} \times V_{Urine\ Rate}$, the numerator of the kinetic equation uses the equivalent expression of $eGFR_{SS} \cdot [Cr]_{SS}$, a surrogate of the creatinine production rate that is assumed to be constant. Since the kinetic situation has 2 [creatinine]s, it uses the average $[Cr]$ in the denominator. The second half of the equation (without unit conversions), $\left(1 - \frac{\Delta[Cr]}{\Delta t} / \frac{\Delta[Cr]}{\Delta t}\Big|_{Max} \right)$, is a "kinetic overlay" that adjusts the clearance calculated by the first half. In severe ATN, for example, the observed