Global Science Research Journals

Global Journal of Medicinal Plant Research

Extended Abstract Open Access

Real-time Measurement of Glomerular Filtration Rate

Richard Solomon, MD, FACP, FASN

University of Vermont Medical Center

Burlington, VT, USA

Abstract: Glomerular filtration rate (GFR) is the most widely used metric of kidney function. The search for an ideal marker of glomerular filtration was ultimately resolved by Homer Smith and his colleagues with the introduction of inulin (1).

- To understand the inherent inaccuracies in the GFR estimating equations.
- To be able to identify when misclassification of a patient's stage of CKD could influence therapeutic and diagnostic decisions.

To be able to identify non-steady state conditions and use novel diagnostic measures to identify early changes in GFR.

Estimating equations lack precision

Increase in misclassification

May not apply to all populations, ethnic groups, age ranges, etc.

Only valid for the populations used in deriving the equations

Need multiple equations

Can't be used in the non-steady state (acute kidney injury)

Short comings of an estimated GFR?

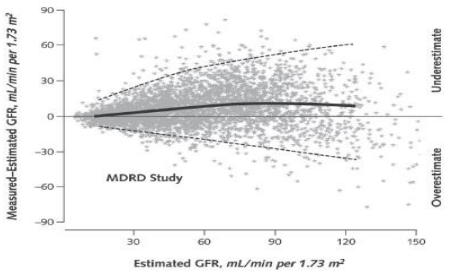
Introduction:

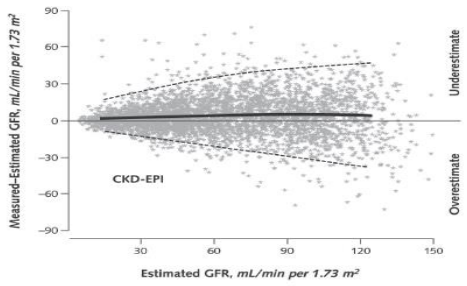
For many years, inulin clearance was considered the gold standard for measurement of GFR but was not practical for clinical medicine. Creatinine was adopted as a surrogate serum marker of GFR and in the past 15 years, equations utilizing serum creatinine, age, gender, and race were developed to estimate GFR in the steady state (2).

Unfortunately, serum creatinine is not an ideal marker of filtration resulting in misclassification of patients (3). In addition, the estimating equations are not validated for the non-steady state making diagnosis and treatment of acute kidney disease (AKI) problematic (4). Because a rise in creatinine in the setting of an acute decrease in GFR takes time (usually 24-48 hours), identification of patients with AKI is delayed resulting in lost opportunities for interventions that would reverse or minimize the injury to the kidney and patient.

Recently, novel technologies using fluorescent serum markers have been developed for measuring GFR accurately and monitoring GFR continuously in a non-invasive manner (5). These technologies are expected to become clinically available in the near future. Opportunities afforded by these techniques will be discussed.

Comparison of MDRD and CKD-EPI





Levey, et. al., Annals of Internal Medicine, 2009, 150: 604-612

Both panels show the difference between mGFR and eGFR versus eGFR.

These two figures speak to the inaccuracy inherent in estimated GFR with either the MDRD or CKD-EPIk equations. As the vertical lines in each figure indicate, the 95% confidence limits at a GFR of 60 ml/min are quite wide. The difference between eGFR at 60 ml/min and mGFR is +-25 ml/min (95% confidence interval)

Short comings of an estimated GFR?

- Depend on measurement of creatinine
    - Different across laboratories (even with IDMS traceable standards)
    - Creatinine affected by renal secretion
    - Creatinine affected by diet, drugs
- Accuracy
    - Estimating equations lack precision
        - Increase in misclassification
- Generalizability
    - May not apply to all populations, ethnic groups, age ranges, etc.
        - Only valid for the populations used in deriving the equations
        - Need multiple equations
- Limited to stable creatinine values
    - Can't be used in the non-steady state (acute kidney injury)

Where is a more accurate determination of renal function (GFR) necessary?

- Steady state
    - Patients who are likely to be under-represented in the samples used to determine estimated GFR.
        - Weights excessively high or low
        - Very elderly
        - Neonates (difficulty with blood assess)
        - Diverse ethnic groups
    - Administration of nephrotoxic drugs
    - Where misclassification may be important.
- Non-Steady state
    - High risk of developing AKI
        - Major surgery
        - ICU patients (25% incidence of AKI)
    - Administration of necessary but potentially nephrotoxic drugs or renally cleared drugs
        - Chemotherapy, antibiotics
        - During CRRT – what is clearance of drug
        - During intermittent dialysis – what is residual renal function

Properties of an Ideal GFR Agent

GFR is optimally measured as the renal clearance of a substance from plasma and is expressed as the volume of plasma cleared of that substance in a unit of time.

- No metabolism
- Not protein bound
- No extra-renal elimination
- Filtered at the glomerulus
- Excreted from body by GFR mechanism only
- Neither reabsorbed nor secreted by the tubule

Methods:

Methods for Measuring GFR

- Urinary clearance
- Plasma clearance
- Nuclear
- Need for instrumentation of bladder to

avoid incomplete empyting.
- Minimum collection period 60-120 minutes
- Continuous infusion of marker vs bracketed serum samples
- Inaccuracies with single sample
- Long duration of multiple sampling at low GFRs
- Use of detector limits availability
- Radiation exposure (limits repeatability)

Fluorescent dextrans (FAST system)

Fluorescent dextrans of different molecular weights can give renal clearance and plasma volumes.

Fluorescent pyrazine (MediBeacon system)

Biocompatibility

Hydrophilic

No protein binding

No metabolism (excreted intact)

No photobleaching

Physiologic pH formulation

Small dose (5 mL)

Highly Soluble

Chemically Stable in solution
at room temperature

Photostable in solution
at room temperature

Large Stokes shift

Results:

Fluorescence of MB-102 = Plasma Concentration of MB-102

- Decay curves identical for plasma concentration and fluorescence.
- Determination of GFR from dose, volume of distribution (extrapolation of decay curve), and exponential decay constant (generated by software).
- Determination of mGFR every 15 minutes.
- Repeatable with redistribution in ECV the only time lag.

Discussions:

What if we could monitor GFR like we monitor O2 saturation?

Might have made diagnosis of AKI much earlier

Earlier institution of KDIGO guidelines

Perhaps more intense/earlier hemodynamic monitoring to maximize cardiac output in the setting of AKI.

GFR is related to organ perfusion.

The only other marker (indirect) of organ perfusion in clinical practice is LACTATE

Positive fluid balance can lead to renal congestion and worsening GFR. Perhaps pressors might have been started instead of fluid administration if it were known that GFR was falling.

Risk of underdosing antibiotics because of high clearances during CRRT

This may be critical in sepsis, promoting ineffective

therapy and development of antibiotic resistance.

Conclusion:

- Novel methods for continuously measuring GFR in real time using fluorescent markers are making their way through the regulatory process.
  - Availability in 2021 likely
  - Initial adoption in the hospital – critical care, operating rooms
- One advantage will be enhanced drug dosing in patients who do not have steady state kidney function.
- Whether such enhanced dosing will improve outcomes is at yet untested.
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Opportunities for mGFR

- Steady state:
  - More accurate assessment of GFR and staging of CKD.
    - Improved chemotherapy dosing
    - Endpoint in clinical trials
  - Determination of RENAL RESERVE.
    - Risk factor for progression of CKD
    - Assessment of recovery after AKI and risk for progression
    - Acceptability for organ donation
  - Response to pharmacologic intervention.
    - Prediction of response to ACEI or ARB
  - Determination of trajectory of

residual renal function in incident dialysis patients.

Summary:

- MB-102 is cleared solely by the kidney
- The plasma clearance of MB-102 matches exactly the plasma clearance of iohexol (the current gold standard for mGFR).
- The plasma clearance of MB-102 matches exactly the fluorescence clearance of MB-102.
- Thus the plasma fluorescence is an adequate marker of GFR.
  - A mGFR can be obtained with 10-15 minutes of recording after equilibrium in ECV is reached (45-60 minutes)
  - mGFR can be monitored continuously for 4 -10 hrs

References:

1. Berliner RW (1995) Homer Smith: His contribution to physiology. J Am Soc Neph 5:1988-1992.
2. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, Kusek JW, Eggers P, VanLente F, Greene T,Coresh J (2009) A new equation to estimate glomerular filtration rate. Ann Int Med 150:604-612.
3. Gaillard F, Courbebaisse M, Kamar N, Rostaing L, Jacquemont L, Hourmant M, Del Bello A, Couzi L, Merville P, Malvessi P, Janbon B, Moulin B, Maillard N, Dubourg L, Lemoine S, Garrouste C, Pottel H, Legendre C, Delanaye P, Mariat C (2019). Impact of estimation versus direct measurement of predonation glomerular filtration rate on the eligibility of potential living kidney donors. Kidney Int 95:896-904.
4. Molitoris BA, Reilly ES (2016). Quantiifying glomerular filtration rates in acute kidney injury: a requirement for translational success. Semin Nephrol 36: 31-41.
5. Bugaj JE, Dorshow RB (2015). Pre-clinical toxicity evaluation of MB-102, a novel fluorescent tracer agent for real-time measurement of glomerular filtration rate. Regul Toxicol Pharmacol 72:26-28.

Dr. Richard Solomon trained in Internal Medicine at the University of California and in Nephrology at Beth Israel Hospital in Boston, MA. He joined the faculty of the University of Vermont in 2002. He is an experienced clinical investigator with interests in hypertension, chronic kidney disease, acute renal failure, and electrolyte disorders. In the area of acute renal failure, Dr. Solomon's work in contrast-induced nephropathy (CIN) remains the pivotal standard for prophylaxis. He has been a thought leader on the adverse long-term effects of CIN on cardiovascular and renal events. He is currently the Chief of the Nephrology Unit in the Department of Medicine at the University of Vermont Medical Center.