CRITICAL CARE

COMMENTARY

Measuring glomerular filtration rate in the intensive care unit: no substitutes please

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See related research by Bragadottir *et al.*, http://ccforum.com/content/17/3/R108

Abstract

Acute kidney injury (AKI), due to its increasing incidence, associated morbidity and mortality, and potential for development of chronic kidney disease with acceleration to end-stage renal disease, has become of major interest to nephrologists and critical care physicians. The development of biomarkers to diagnose AKI, quantify risk and predict prognosis is receiving considerable attention. Yet techniques to accurately assess functional changes within patients still rely on the use of an insensitive marker (creatinine), creatinine-based estimating equations and unreliable urinary tests. Therefore, it is critical that functional tests be developed and used in combination with biomarkers, thus allowing improved care in AKI and chronic kidney disease patient populations.

Bragadottir and colleagues found utilization of glomerular filtration rate (GFR) estimating equations of limited value, no value or perhaps even negative value in intensive care unit (ICU) acute kidney injury (AKI) patients [1]. They confirmed the limited, inaccurate and highly variable data obtained from urinary creatinine collections to quantify the GFR. They acknowledge this had been shown before and point to inaccurate urine collections and variable release of creatinine from muscle as problems [2-4]. Unfortunately, the available tests to quantify the GFR utilize a single-compartment model that requires several hours for equilibration between the plasma volume and extracellular fluid space. In addition, they require laboratory determinations that are complex, sensitive to user error, time consuming and expensive.

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The use of serum creatinine, and the accompanying equations to estimate the GFR in patients with stable kidney function, has been beneficial in longitudinal population studies where trends are followed and the known wide variation between calculated and determined GFRs is acceptable. The necessity of a plasma equilibrium state for creatinine, based on the stable release of creatinine from muscle and stable removal by the kidney via the GFR, is well known in these situations. In states of AKI, however, these necessary parameters do not hold and thus it is predictably impossible to use serum creatinine or equations based on serum creatinine.

Further complicating the use of these parameters in the acute situation is the availability of renal reserve. The renal reserve represents the ability of the normal kidney to increase the GFR following specific challenges such as a high-protein meal, early diabetes, unilateral nephrectomy or progressive loss of kidney function [5]. Renal reserve can be >50% of baseline unstimulated kidney function, thus increasing the GFR from 100 ml/minute/1.73 m^2 to >150 ml/minute/1.73 m^2. Renal reserve may therefore be one reason why the GFR can fall to 50% of normal values prior to detection based on a rise in serum creatinine. This observation has made the use of serum creatinine insensitive as a marker of development of chronic kidney disease and is in part why the estimating equations for the GFR are not useful above a GFR of 50 to 60 ml/minute/1.73 m^2. In theory, therefore, a patient could have lost up to 67% of their baseline total GFR, going from a potential GFR of 150 ml/minute/1.73 m^2 to one of 50 ml/minute/1.73 m^2 prior to a change in serum creatinine (Figure 1). We know very little about renal reserve in AKI.

An additional problem with serum creatinine as a marker of kidney function in cases of AKI is the slow rate of rise to an equilibrium state. In a noncatabolic 70 kg patient, if you were to remove both kidneys the serum creatinine would rise by only 1 mg/dl/day. Thus,

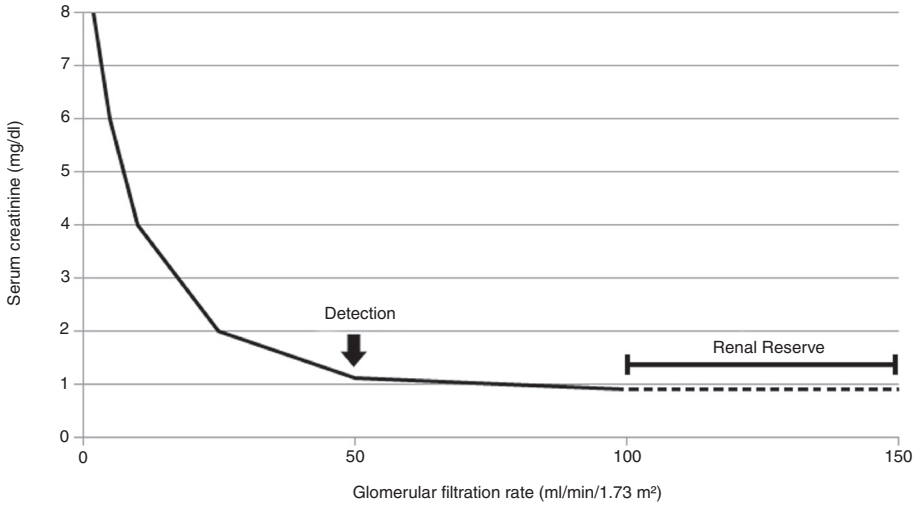

Figure 1 Serum creatinine is an insensitive marker of the glomerular filtration rate. With loss of the glomerular filtration rate (GFR) the renal reserve may be first lost, reducing the maximally stimulated GFR. Thereafter, as the GFR is lost the serum creatinine (SCr) does not rise until the GFR is reduced to around 50 to 60 ml/minute/1.73 m^2. Therefore, up to two-thirds of the patient's original GFR has been lost before changes in SCr occur.

1 day post bilateral nephrectomy the patient's serum creatinine would be 2 mg/dl, on day 2 it would be 3 mg/dl, and so on, even though the patient has zero GFR. Patients with severe AKI therefore sit in the ICU waiting for blood chemistries, or their volume status, to rise to renal replacement levels, all the while being in a state we believe requires renal replacement therapy for appropriate support. Add to this the other factors known to confound serum creatinine as a marker of the GFR and is there any wonder why its use in the ICU, where accurate quantitative data are a must, is resulting in less than maximal care of the patient [6-10].

On a brighter note, commercial attempts have been initiated to develop a rapid, sensitive, reproducible, affordable and user-friendly GFR technique [9,11]. Clearance of a freely filterable water-soluble molecule is being used with either noninvasive or minimally invasive approaches. Both one-compartment and two-compartment models are being developed, with two-compartment approaches offering a more rapid result because equilibration with the extracellular fluid is not needed [12]. FAST BioMedical (Indianapolis, IN, USA) has recently completed a phase I, single-blind, dose escalation study in normal patients with satisfactory results (unpublished observation; see Competing interests statement).

Perhaps a more intriguing question for the clinician to now consider is, when available, how will a GFR test be used to advance care in the hospitalized patient? To commercialize such a product there must be defined clinical pathways resulting in meaningful, cost-effective and patient-beneficial outcomes that can be standardized for general use. In AKI, functional confirmation and quantification of the severity of injury would allow the physician to determine the immediate need for renal replacement therapy. Additionally, the response to hydration or pressor therapy could be quantified with a second test post-therapy. Weaning from continuous veno-venous hemofiltration therapy or movement of the patient to the ward, based on the return of kidney function that is now quantifiable, may minimize valuable days in the ICU. Knowing the actual GFR for drug dosing of renally cleared drugs or nephrotoxins may provide more reliable serum levels. Accurate GFRs would also accurately identify patients with low GFRs requiring preventative therapies prior to use of agents such as radiocontrast or gadolinium.

The field of nephrology has lagged in the development of diagnostic technology. However, it now seems time to turn attention to the care of the AKI and chronic kidney disease patient in an effort to minimize, or at least forestall, the development of end-stage renal disease and requirement for chronic renal replacement therapy. Individualization of patient care will come through innovation and its careful application. The cost of such development and utilization can be easily rationalized based on the patient and societal costs of end-stage renal care of chronic dialysis patients.

Abbreviations

AKI: Acute kidney injury; GFR: Glomerular filtration rate; ICU: Intensive care unit.

Competing interests

BAM is a co-founder, part owner, and medical director of FAST Biomedical (Indianapolis, IN, USA).

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