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Kinetic estimated glomerular filtration rate and acute kidney injury in cardiac surgery patients☆

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ABSTRACT

Purpose: To determine how a formula to estimate kinetically changing glomerular filtration rate (keGFR) relates to serum creatinine changes and to compare the discriminatory ability of keGFR to that of perioperative change in serum creatinine to predict acute kidney injury (AKI) and mortality.
Materials and Methods: Retrospective cohort study at a single-tertiary-care Midwestern university hospital of 4022 patients admitted to the intensive care unit between January 2006 and January 2012 immediately after cardiac surgery.
Measurements and Main Results: Of 4022 patients, 1031 (25.6%) developed at least AKI stage 1 and 1106 (27.5%) developed AKI-min. Patients who developed AKI stage 1 or AKI-min had a greater decrease in keGFR, both by absolute amounts and by percentage. After adjusting for other factors with logistic regression, keGFR had good discrimination (c statistic = 0.787 and 0.749, respectively) in predicting AKI and operative mortality.
Conclusion: Despite no change in immediate perioperative serum creatinine levels, keGFR fell and this predicted subsequent AKI. Using keGFR enables identification of patients who, despite unchanged postoperative creatinine, incur clinically significant kidney injury based on reduction in GFR and increased mortality.

1. Introduction

Acute Kidney Injury (AKI) after cardiac surgery is associated with increased health care costs, longer intensive care unit (ICU) stays, and a higher incidence of complications including both short- and long-term mortality [1–4]. The development of AKI after cardiac surgery is relatively common, with an incidence between 1% and 30% depending on both the type of cardiac surgery performed and the diagnostic criteria used, with the risk of mortality increasing with severity of AKI [5–12]. Even a 0.1- to 0.5-mg/dL increase in postoperative creatinine has been associated with a 3-fold increase in relative risk of death, and increases greater than 0.5 mg/dL are associated with greater than 18-fold increase in 30-day mortality [10,11].

Although direct measurement of glomerular filtration rate (GFR) (by inulin, iohexal, EDTA, or iothalamate) is considered the criterion standard for quantifying renal function, this is costly, subject to measurement errors, and not routinely available for clinical use [13]. Creatinine, a metabolite of creatine phosphate, is freely filtered by the glomerulus in proportion to GFR. Although a small amount of creatinine is actively secreted by the peritubular capillaries leading to a small overestimate of GFR, measurement of urine and serum creatinine to calculate creatinine clearance (CrCl) as a surrogate of GFR is the most common technique for measuring renal function in stable patients. However, because of inaccuracies in fluid collection and timing of the samples, this test is rarely performed in the ICU. Instead, a single measurement of serum creatinine is frequently used as a measure of renal filtration function in the ICU because serum creatinine is inversely proportional to CrCl. Although this may be valid in steady-state conditions, this typically does not apply to critically ill patients. Consequently, acute changes in GFR may not be reflected by the serum creatinine due to the time required for creatinine to accumulate and equilibrate. In addition, administration and retention of fluids will dilute creatinine, whereas hemorrhage will cause loss of serum creatinine. These factors, which occur commonly in critically ill patients, produce inaccurate estimations of CrCl.

Several publications have attempted to create a "kinetic" estimated GFR (keGFR) equation to estimate CrCl or GFR in the non–steady-state using 2 creatinine measurements and fluid balance; others have used 2 compartment models to accurately estimate CrCl in the setting of fluctuating renal function, thereby facilitating earlier classification of AKI than by a creatinine-based approach, or the principles of mass balance [14–16]. These mass balance equations have the potential to provide clinically relevant real-time values of GFR without the need for timed urine collections.

The goals of this study were to compare keGFR in the immediate postoperative period with changes in serum creatinine and to assess each of these variables in predicting the development of AKI within the first 3 days after cardiac surgery. We hypothesized that by applying kinetic

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Equation A

$$Glomerular\ filtration\ rate = \frac{creatinine\ excreted}{mean\ serum\ creatinine} \div time$$

Equation B

$$Creatinine\ mass\ at\ start\ of\ surgery = volume\ of\ distribution \times serum\ creatinine\ at\ start\ of\ surgery$$

Equation C

$$Creatinine\ mass\ on\ arrival\ in\ ICU = creatinine\ mass\ at\ start\ of\ surgery + creatinine\ produced - creatinine\ excreted\ in\ urine$$

Rearranging Equation C produces Equation D

$$Creatinine\ excreted\ in\ urine = creatinine\ mass\ at\ start\ of\ surgery - creatinine\ mass\ on\ arrival\ in\ ICU + creatinine\ produced$$

Equation E [20]

$$Volume\ of\ distribution = weight \times \frac{(.4L)}{kg} \times \frac{10dL}{L}$$

Equation F

$$Creatinine\ mass\ at\ ICU\ arrival = \left(volume\ of\ distribution + intraoperative\ fluid\ balance\right) \times serum\ creatinine\ at\ ICU\ arrival$$

Substituting Equation D into Equation A and rearranging produces Equation G

$$keGFR = \frac{creatinine\ produced + creatinine\ mass\ at\ start - creatinine\ mass\ on\ arrival}{mean\ serum\ creatinine} \div time$$

Equation H [20, 21, 22]

$$Creatinine\ produced\ \left(\frac{mg}{day}\right) = weight \times \left[(29.305 - .23 \times age) \times \frac{1344.4 - 43.76 \times \frac{Cr_s + Cr_a}{2}}{1344.4 - 43.67 \times 1.1}\right] \times .95 \times [.9\ if\ female]$$

Substituting Equations B, E, F, and H into G and rearranging yields Equation I

$$keGFR = \frac{{}^{100\,mL}/_{dL} \times \left[Equation\ H \times \frac{Time}{{}^{1440\,min}/_{day}} + {}^{4\,dL}/_{kg} \times weight \times \left(Cr_s - Cr_a\right) - FB \times Cr_a\right]}{\frac{Cr_s + Cr_a}{2}} \div time$$

Fig. 1. Cr (creatinine) is in mg/dL (Cr_s is serum creatinine at the start of surgery and Cr_a on arrival in the ICU), weight is the minimum of actual or ideal weight in kg, keGFR and GFR are in mL/min, time is the time in minutes between the start of surgery and the obtaining of serum creatinine level in the ICU postoperatively, and FB is the intraoperative fluid balance in dL. Extracellular fluid volume was used instead of total body water because prior work by Jelliffe [20] found a superior fit in a regression model. All GFRs were normalized to 1.73-m^2 body surface area. Calculations were performed using Excel (Microsoft, Redmond, WA) [21,22].

methods for estimating GFR prior to achieving a new steady-state for creatinine, we would be able to predict AKI before it can be diagnosed by changes in serum creatinine levels. Furthermore, we hypothesized that patients with a decrease in keGFR would have a higher mortality risk. This is based on studies that demonstrate that no change or minimally elevated creatinine levels, below the levels usually used to define AKI [17], are associated with increased mortality after cardiac surgery [11,12].

Table 1
Demographics and clinical characteristics by AKI classification

Patient characteristics	AKI stage 1 (n = 1030)		AKI-min (n = 1106)		AKI-none (n = 1883)		ANOVA, *P*
	Mean	SD	Mean	SD	Mean	SD	
Age (y)	63	14	62	14	61	14	<.001
Body mass index (kg/m^2)	30.2	7.2	29.3	6.3	28.6	5.7	<.001
	n	%	n	%	n	%	Fisher's exact p
Male	684	66	721	65	1189	63	.186
Hypertension	761	74	741	67	1139	61	<.001
Diabetes mellitus	266	26	246	22	358	19	<.001
Cerebrovascular disease	125	12	109	10	182	10	.098
Congestive heart failure	317	31	235	21	366	19	<.001
Peripheral vascular disease	84	8	64	6	116	6	.060
Chronic lung disease	185	18	165	15	252	13	<.001
Death	62	6.0	13	1.2	16	0.8	<.001

Forty-five patients are missing body mass index data. ANOVA indicates analysis of variance.

2. Materials and methods

This retrospective cohort study used in-patient data collected at a large, tertiary care university hospital and was approved by the institutional review board which waived patient consent because all patient data were de-identified. All adult patients undergoing cardiac surgery from January 4, 2006, to January 5, 2012, requiring postoperative admission to the ICU were eligible. Patients were excluded if baseline creatinine was unavailable, postoperative creatinine data were unavailable within the first 3 postoperative days, or the patient was dependent on dialysis preoperatively. The most recent preoperative serum creatinine was used to derive a preoperative estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula [18]:

$$GFR_{mL/min} = 175 \text{ x Serum Creatinine}^{-1.154} \text{ x Age}^{-0.203} \text{ x [1.212 if Black] x [0.742 if Female], with age in years and creatinine in mg/dL.}$$

Compared with ^{125}I − iothalamate, the median absolute error (interquartilerange) of the MDRD GFR formula is 0.2 (7.7) mL/min per 1.73m^2 [18]

Kinetic estimated glomerular filtration rate was calculated using an estimate of creatinine production over time and adjusted for fluid shifts