ORIGINAL ARTICLE

Estimation of Kinetic Glomerular Filtration Rate in Patients with Decompensated Heart Failure

Cálculo dinámico del filtrado glomerular en los pacientes con insuficiencia cardíaca descompensada

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ABSTRACT

Background: The coexistence of decompensated heart failure (DHF) and acute renal failure (ARF) is associated with longer hospital stay and greater mortality.
Objectives: The aim of this study was to evaluate whether kinetic glomerular filtration rate (KeGFR) estimated with Chen's equation can predict the development of ARF or mortality during hospitalization in patients with DHF.
Methods: We conducted a retrospective study of consecutive patients with estimated kinetic glomerular filtration rate using serum creatinine levels on admission and at 24 hours. The primary endpoint was a composite of ARF or mortality, and a ROC curve was built to find the cutoff value with the best sensitivity and specificity to predict events. Acute renal failure was defined according to the KDIGO guideline. Patients were followed-up throughout hospitalization and those with a history of chronic renal failure were excluded from the study.
Results: Among 813 patients, 190 were excluded due to chronic renal failure and 608 patients were analyzed. Median age was 81 years (IQR 25-75%: 73-87) and 48% were men; 25.5% were diabetics, 76% had hypertension, 19.4% had history of prior myocardial infarction and 46.8% presented left ventricular systolic dysfunction defined as left ventricular ejection fraction <45%. Median creatinine level on admission was 1.05 mg/dl. The incidence of the composite event was 41.1%. Age, sex and comorbidities were similar in patients with and without the composite event, but KeGFR was significantly lower in this group of patients (median: 50.7 ml/min vs. 57.9 ml/min, p<0.01) and resulted an independent predictor of mortality. The analysis of the ROC curve revealed that a cutoff point of 60 ml/kg/min for KeGFR (AUC 0.60) had the best diagnostic accuracy to predict the composite event and was present in 58.9% of the patients. Age, female sex, hypertension and diabetes were predictors of the composite event.
Conclusions: Kinetic glomerular filtrate rate can be used as an independent predictor of the composite event, but has no clinical relevance due to its low specificity.

Key words: Heart failure – Renal failure - Prognosis

RESUMEN

Introducción: La coexistencia de insuficiencia cardíaca descompensada (ICD) e insuficiencia renal aguda (IRA) conlleva internaciones más prolongadas y, en algunos casos, mayor mortalidad.
Objetivos: Evaluar si la tasa de filtrado glomerular dinámico (TFGD) calculada mediante la fórmula de Chen permite predecir el desarrollo de IRA o muerte durante la internación en pacientes con ICD.
Material y métodos: Estudio retrospectivo de pacientes consecutivos. Se calculó la TFGD utilizando los valores de creatinina del ingreso y a las 24 h. Se realizó una curva ROC para hallar el punto que con mejor sensibilidad y especificidad predijera eventos. Se evaluó un punto final de evento combinado (EC) definido como el desarrollo de IRA o muerte. Se definió la IRA de acuerdo a la guía KDIGO. El seguimiento fue hospitalario. El criterio de exclusión principal fue la existencia de antecedentes de insuficiencia renal crónica.
Resultados: De un total de 813 pacientes, 190 fueron excluidos por tener insuficiencia renal crónica. Se analizaron 608 pacientes. Edad (mediana): 81 años (RIC 25-75%: 73-87), hombres: 48%, diabéticos: 25,5%, hipertensos: 76%, infarto previo: 19,4%, disfunción sistólica (Fey<45%): 46,8%, creatinina de ingreso (mediana): 1,05 mg/dl. La incidencia de EC fue de 41,1%. La edad, el sexo y la presencia de comorbilidades no incidieron en la tasa de presentación de EC, pero la TFGD de este grupo de pacientes fue significativamente menor (mediana: 50,7 ml/min, vs. 57,9 ml/min, p<0,01) y esta variable fue un predictor independiente de mortalidad. El mejor valor por curva ROC para EC de la TFGD fue 60 ml/min (ABC 0,60) y estuvo presente en el 58,9% de los pacientes. Fueron predictores de ello la edad, el sexo femenino y la presencia de HTA y de diabetes.
Conclusiones: La TFGD resulta ser un predictor independiente de EC intrahospitalarios en la ICD; sin embargo, presenta escasa relevancia clínica por su baja especificidad.

Palabras clave: Insuficiencia cardíaca- Insuficiencia renal- Pronóstico

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INTRODUCTION

Decompensated heart failure (DHF) is one of the most relevant causes of hospitalization in the coronary care unit and its prevalence is expected to increase as life expectancy is higher. (1) Its treatment includes diuretics to produce negative fluid balance, both if heart failures is due to left ventricular systolic as diastolic dysfunction.

In some cases, DHF may coexist with renal dysfunction, which may be present on admission or develop during hospitalization. (2) Acute renal failure (ARF) as a complication of DHF during hospitalization is associated with longer hospital stay and greater mortality. (3-5) The possibility of identifying patients at risk for ARF or mortality during hospitalization could help to change the treatment and the course of the disease. So far, there are no variables to accurately predict the development of ARF. The aim of this study was to evaluate whether the use of a new equation to estimate kinetic glomerular filtration rate using serum creatinine measurements on admission and at 24 h, could predict the development of adverse events (ARF and mortality) during hospitalization.

METHODS

We conducted an observational and retrospective study of patients with a diagnosis of DHF consecutively admitted to the coronary care unit of two centers in the City of Buenos Aires. The inclusion criterion was defined as two creatinine values obtained on different days: on admission and 24 hours after hospitalization. Demographic variables, coronary risk factors, presence of comorbidities and history of previous diseases were analyzed. Serum creatinine levels ≥1.5 mg/dl and ≥2 mg/dl were recorded. Creatinine clearance was calculated using the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Kinetic glomerular filtration rate (KeGFR) was calculated according to Chen's equation (6):

$$\text{KeGFR} = \frac{\text{Cr1 x GFR}}{(\text{Cr1}+\text{Cr2})/2} \times \left(\frac{1 - 24 \times (\text{Cr2} - \text{Cr1})}{\Delta t \times \text{Max}\Delta\text{Cr/day}}\right)$$

where Cr1 and Cr2 are serum creatinine levels on admission and at 24 h, respectively; GFR is the glomerular filtration rate calculated by the MDRD equation with the creatinine level on admission; Δt is the time difference in hours between both creatinine determinations; and MaxΔCr/day refers to the maximum increase in plasma creatinine level that can occur per day if renal function is completely lost (mean value for most adults: 1.5 mg/dl). This value can be easily calculated using an application for smartphones (https://qxmd.com/calculate/calculator_367/kinetic-egfr-kegfr).

The primary endpoint was a composite of ARF or all-cause mortality during hospitalization. Acute renal failure was defined according to the KDIGO clinical practice guideline as an increase in serum creatinine ≥0.3 mg/dl or ≥50% from baseline. (7)

Patients who did not have both creatinine determinations or those with a history of chronic renal failure or who were in dialysis or were referred to another center for clerical reasons were excluded from the study.

Statistical analysis

Continuous variables are expressed as mean and standard deviation, or median and interquartile range 25-75%, according to their distribution. Discrete variables are expressed in percentage. Continuous variables with normal and non-gaussian distribution were compared using Student's t test or the Wilcoxon rank sum test, respectively. Discrete variables were compared using the chi-square test or Fisher's exact test.

Univariate and multivariate Cox regression analyses were performed in order to identify independent predictors of ARF and in-hospital mortality. A p value <0.05 was considered statistically significant. A ROC curve was constructed with the KeGFR levels to find the value with the best sensitivity and specificity to predict the composite event. Then, univariate and multivariate analyses were performed to identify the independent predictors of KeGFR resulting from the ROC curve. All the calculations were performed using Stata 21.0 software package.

Ethical considerations

The study was evaluated and approved by the Ethics and Scientific Committees of both institutions.

RESULTS

Between May 2010 and May 2017, 813 patients were hospitalized in two coronary care units due to DHF. After excluding 190 patients with chronic renal failure and 15 patients without both determinations of serum creatinine, 608 patients were included in the analysis. Median age was 81 years (IQR 25-75%: 73-87) and 48% were men; 25.5% were diabetics, 76% had hypertension, 19.4% had prior history of myocardial infarction and 46.8% presented left ventricular systolic dysfunction defined as left ventricular ejection fraction (LVEF) <45% by echocardiography. Median creatinine level on admission was 1.05 mg/dl.

In-hospital mortality was 4.1% and the incidence of ARF during hospitalization was 40.5%. The incidence of the composite endpoint was 41.2%.

Patients who developed ARF or died during hospitalization did not differ in age, sex, comorbidities and GFR calculated by MDRD and CKD-EPI. Only KeGFR was significantly lower in those patients who developed ARF/mortality (median: 50.7 ml/min vs. 57.9 ml/min; p <0.01) (Table 1).

The analysis of the ROC curve revealed that a cut-off point of 60 ml/kg/min for KeGFR had the best diagnostic accuracy to predict events, with an area under the curve (AUC) of 0.60 (0.55-0.64, p<0.01), a sensitivity of 67% and a specificity of 46%.

In 205/608 patients (41.1%) KeGFR was ≥60 ml/min and <60 ml/min in 358/608 (58.9%). The group with KeGFR <60 ml/min were mostly women (58.6% vs. 42.8%, p<0.01) and older patients (median age: 83 years vs. 76 years in the first group; p <0.001). Moreover, in these patients, the prevalence of hypertension was greater (79.3% vs. 71. 2%, p=0.011) and with similar incidence of diabetes (23% vs. 29.2%, p=0.051) and systolic dysfunction (45.2% vs. 49%, p=0.18) than in those with KeGFR ≥60 ml/min.

Glomerular filtration rate estimated with the MDRD and CKD-EPI equations using serum creatinine levels on admission, was significantly lower in patients with KeGFR <60 ml/min/1.73 m2 (Table 2). In-hospital mortality was 4.75% in patients with KeGFR <60 ml/min versus 3.2% in the group with KeGFR ≥60 ml/min (p=0.17) and development of ARF was 46.1% versus 32.4%, respectively (p <0.001). In the multivariate model to predict KeGFR <60 ml/min/1.73 m2, which included age, female sex, presence of hypertension and diabetes and GFR on admission calculated by MDRD and CKD-EPI <60 ml/min/1.73 m2, age and low GFR on admission were identified as independent predictors (Table 3).

DISCUSSION

Decompensated heart failure (DHF) is one of the most common causes of hospitalization in the coronary care unit and is associated with longer hospital stays, re-hospitalizations and high in-hospital and follow-up mortality, imposing a huge economic burden to the health care systems. (8)

Decompensated HF may coexist with renal failure, (9, 10) which may be present on admission or develop during hospitalization. (11) A large meta-analysis showed that both presentations of renal failure are associated with adverse outcome (4) that is worse when renal impairment is greater. (5) However, worsening renal function in the setting of negative fluid balance

Table 1. Univariate analysis for the composite event (ARF/mortality)

	Event n: 250 (41.12%)	No event n: 358 (58.88%)	p	OR (95% CI)
Age, (years), median (IQR)	82 (72-87)	80 (73-87)	0.68	
Men	49.2%	46.9%	0.29	0.91 (0.66-1.26)
DBT	26.5%	24.8%	0.32	1.09 (0.75-1.57)
HT	76.4%	75.7%	0.42	1.03 (0.71-1.51)
Systolic dysfunction	45.5%	47.5%	0.31	0.92 (0.66-1.27)
History of cardiovascular disease (AMI, CABGS, PCI, stroke)	35.6%	37.15%	0.34	0.93 (0.66-1.3)
MDRD (ml/min/1.73 m2), median (IQR 25-75%)	61.7 (49.5-80.3)	61.5 (46.9-76.5)	0.32	
MDRD <60 ml/min/1.73 m2	46.8%	47.8%	0.4	0.96 (0.69-1.32)
CKD-EPI (ml/min/1.73m2), median (IQR 25-75%)	56.4 (44.3-77)	57.5 (43-74.4)	0.69	
CKD-EPI <60 ml/min/1.73m2	56%	55.6%	0.46	1.01 (0.73-1.4)
KeGFR (ml/min), median (IQR 25-75%)	50.7 (38.3-66.4)	57.9 (45.1-74.4)	<0.01	
KeGFR <60 ml/min	67.2%	53%	<0.01	1.81 (1.29-2.53)
Creatinine levels on admission (mg/dl), median (IQR)	1.025 (0.9-1.3)	1.075 (0.9-1.3)	0.75	
Creatinine levels on admission ≥1.5 mg/dl	12%	11.45%	0.41	1.05 (0.36-1.74)
Creatinine levels on admission ≥2 mg/dl	4.4%	3.35%	0.25	1.32 (0.57-3.05)

HT: Hypertension. DBT: Diabetes. AMI: Acute myocardial infarction. CABGS: Coronary artery bypass graft surgery. PCI: Percutaneous coronary intervention. Systolic dysfunction: Left ventricular ejection fraction <45%.

Table 2. Characteristics of the population according to kinetic glomerular filtration rate ≥ or <60/ml/kg/min

	KeGFR ≥60 ml/min	KeGFR <60 ml/min	p	OR (95% CI)
Age (years), median (IQR 25-75%)	76 (67-83)	83 (78-88)	<0.001	
Female sex	107 (42.8)	210 (58.7)	<0.01	1.89 (1.36-2.63)
HT	178 (71.2)	284 (79.3)	0.01	1.55 (1.06-2.25)
DBT	73 (29.2)	82 (23)	0.051	0.72 (0.5-1.04)
History of cardiovascular disease (AMI, CABGS, PCI, stroke)	94 (37.6)	128 (35.75)	0.35	0.92 (0.66-1.29)
LVEF < 45%	119 (49)	160 (45.2)	0.18	0.85 (0.61-1.19)
Creatinine levels on admission, mg/dl	0.9 (0.75-1)	1.2 (1-1.45)	0.001	
MDRD < ml/min/1.73 m2	20 (8)	268 (75)	0.0001	34.2 (20-57)
CKD-EPI <60 ml/min/1.73 m2	38 (15.2)	301 (84%)	0.0001	29.5(19-46)
In-hospital mortality	8 (3.2)	17 (4.75)	0.17	1.5 (0.64-3.55)
ARF	81 (32.4)	165 (46.1)	<0.001	1.73 (1.27-2.49)
Mortality/ARF	82 (32.8)	168 (46.9)	<0.001	1.81 (1.29-2.53)

HT: Hypertension. DBT: Diabetes. AMI: Acute myocardial infarction. CABGS: Coronary artery bypass graft surgery. PCI: Percutaneous coronary intervention. LVEF: Left ventricular ejection fraction <45%. ARF: Acute renal failure.

due to DHF is not necessarily associated with an adverse clinical outcome. (12-14)

In our study, in-hospital mortality was 4.1%, similar to that of the large American registries ADHERE, (15) which included 65,000 patients (4%), and OPTIMIZE-HF, (16) with 48,000 patients (3.4%). The prevalence of ARF in our analysis was 40.5%. In other series, it ranges between 23% (17) and 60%; (18) however, the prevalence of ARF may vary according to the definitions used and the age group analyzed, as it is more prevalent in older patients. (19) Median age was 82 years in our population, higher than the one reported in previous Argentine registries with an average of 70 years. (20) Undoubtedly, renal failure is an undesirable event that prolongs hospital stays and hampers titration of medications which are important in the treatment of patients with DHF, regardless of its actual prognostic value.

The possibility of predicting which patients will develop ARF would be extremely useful to prevent it. In this sense, several studies have demonstrated the association between clinical characteristics such as age or diabetes and ARF, but none of them can be modified. Among the factors that could probably be modified: the degree of negative balance, diuretics doses or the way of administration depend on each patient; therefore, no scientific study would be able to analyze or compare these factors. Measurement of serum or urine biomarkers as cystatin C or neutrophil gelatinase-associated lipocalin (NGAL) have failed to fulfill this role. (21-26) Thus, the predictive capacity of two easily acquired blood samples, obtained on consecutive days, would be very useful.

In chronic patients, the use of creatinine values alone to diagnose renal failure has already been replaced by estimating GFR using equations, (3) as significant reductions in GFR may occur with serum creatinine levels within normal ranges. These equations have been described and validated in outpatient populations, with stable creatinine levels and without ascites or edema. This setting is different from the one of patients hospitalized for DHF, in which creatinine levels and GFR may vary according to the extent of venous congestion, cardiac output, neurohormonal activation, inflammation, the effect of negative fluid balance with diuretics or the use of potentially nephrotoxic medications, among other factors. (27, 28)

Several attempts have been made to estimate a dynamic clearance. (6, 29-32) These equations are based on the creatinine mass balance principle, which relates creatinine generation to creatinine excretion and is evidenced by a change in serum creatinine levels over time and have different mathematical calculations. Chen at al. developed an equation to calculate KeGFR in a simple way using easily available determinations. (18) The equation, also available in smartphones applications, (33) seems to be a reasonable way to evaluate changes in renal function in the acute scenario. This equation has been evaluated in other clinical settings, as cardiovascular surgery (34) or in intensive care unit patients, (35, 36) with good results, and is being incorporated into practice guidelines for the management of kidney diseases. (37, 38)

In our study, KeGFR proved to be capable of identifying patients who would develop the composite event during hospitalization with statistical significance ($p < 0.01$). However, median KeGFR was 50.7ml/kg/min (IQR 25-75%: 38.3-66.4) in the group with ARF/death vs. 57.5 ml/kg/min (IQR 25-75%: 44.7-72.3). This overlap of values in the confidence intervals means that, although the difference found is significant, it lacks clinical relevance. (39) In the same sense, the area under the ROC curve of 0.6 also reflects a poor correlation with events, with a sensitivity of 67% and a specificity of 43%. In other words, we could detect almost 7 out of 10 patients who would develop ARF/mortality, but we would be wrong about the prognosis in more than 50% of cases. Unfortunately, there are still no factors capable of eventual modification to predict the development of ARF/mortality in patients hospitalized for DHF.

Study limitations

Perhaps the major limitation is the lack of a gold standard to define ARF at present and the need to use serum creatinine levels for the definition. The fact that two determinations of serum creatinine are needed means this equation cannot be applied to patients dying within the first 24 hours after admission.

CONCLUSIONS

Kinetic glomerular filtrate rate is a simple and affordable variable that can be used as an independent predictor of the development of renal failure and in-hospital mortality in patients hospitalized for DHF, but has no clinical relevance due to its low specificity.

Variables	OR	95% CI	p
Age (per year)	1.03	1.01-1.05	<0.002
Female sex	1.15	0.72-1.85	0.056
HT	1.12	0.65-1.94	0.67
DBT	0.91	0.52-1.54	0.70
MDRD < 60 ml/min/1.73 m2	8.85	4.2-18.6	<0.001
CKD-EPI <60 ml/min/1.73 m2	4.95	2.55-9.57	<0.001

HT: Hypertension. DBT: Diabetes.

Table 3. Multivariate analysis to predict KeGFR <60 ml/min

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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