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Hidden renal dysfunction causes increased in-hospital mortality risk after coronary artery bypass graft surgery

Insuficiência renal oculta acarreta risco elevado de mortalidade após cirurgia de revascularização miocárdica

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Abstract

Introduction and Objectives: **Preoperative chronic renal dysfunction is an independent predictor of mortality in cardiac surgery. As normal range serum creatinine is not representative of normal renal function, we compared mortality rates, total hospital stay and post-surgical hospital stay for patients who underwent isolated coronary artery bypass surgery with serum creatinine ≤ 1.5mg/dL as to their estimated creatinine clearance, normal or impaired.**

Methods: **In 4,765 patients submitted to coronary artery bypass surgery between January/1996 and June/2004, the creatinine clearance was estimated by the Cockroft-Gault equation. Impaired renal function was considered as a creatinine clearance <60 mL/min/1.73m² (chronic renal disease stage 3 - National Kidney Foundation-USA). In-hospital mortality, total hospital stay, and post-surgical hospital stay were compared.**

Results: **4,688 patients had the required data, and 4,403 presented serum creatinine ≤ 1.5mg/dL - 3,177 with creatinine clearance ≥ 60mL/min (Group A), and 1,226 with <60mL/min (Group B). Group B patients had significantly higher total hospital stay and post-surgical hospital stay than those in Group A (respectively 2.85 and 1.79 more days - *P*<0.0001). Relative risk of in-hospital death was 2.09 to Group B (95%CI:1.54-2.84) when compared to Group A.**

Conclusions: **More than one quarter of the patients with serum creatinine ≤ 1.5mg/dL had creatinine clearance <60 mL/min. This expressive number of patients, that would not have their renal dysfunction detected by the serum creatinine parameter alone, had double the risk of death, longer total hospital stay and post-surgical hospital stay than the other patients with serum creatinine ≤ 1.5mg/dL.**

Descriptors: **Myocardial Revascularization. Hospital Mortality. Renal Insufficiency, Chronic. Risk Factors. Creatinine.**

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Resumo

Introdução e Objetivos: **Insuficiência renal crônica pré-operatória é fator preditivo independente para mortalidade em cirurgia cardíaca. Como creatinina sérica normal não representa obrigatoriamente função renal normal, comparamos as taxas de mortalidade, de permanência hospitalar total e de permanência hospitalar pós-operatória em pacientes submetidos à cirurgia de revascularização miocárdica isolada com creatinina ≤ 1,5 mg/dL, de acordo com a depuração estimada, normal ou alterada.**

Métodos: **Em 4.765 pacientes submetidos à revascularização cirúrgica do miocárdio entre janeiro/1996 e junho/2004, a depuração da creatinina foi estimada através da equação de Cockcroft-Gault. Considerou-se função renal alterada uma depuração da creatinina <60 mL/min/1,73m² (doença renal crônica estágio 3 - *National Kidney Foundation-EUA*). Mortalidade hospitalar, permanência hospitalar total e permanência hospitalar pós-operatória foram comparadas.**

Resultados: **4.688 pacientes tinham disponíveis os dados necessários para a análise e 4.403 apresentavam creatinina plasmática ≤ 1,5 mg/dL - 3.177 com depuração da creatinina ≥ 60 mL/min (Grupo A) e 1.226 com <60 ml/min (Grupo B). Pacientes no Grupo B apresentaram permanência hospitalar total e permanência hospitalar pós-operatória significativamente maiores do que no Grupo A (respectivamente 2,85 e 1,79 dias a mais - *P*<0,0001). Risco relativo de morte intra-hospitalar foi de 2,09 no Grupo B (IC 95%:1,54-2,84) comparado ao Grupo A.**

Conclusões: **Mais de 1/4 dos pacientes com creatinina ≤ 1,5 mg/dL apresentavam depuração inferior a 60mL/min. Esse expressivo número de pacientes, os quais não teriam sua disfunção renal detectada pela creatinina sérica isoladamente, apresentaram o dobro do risco de mortalidade, e permanência hospitalar total e pós-operatória maiores do que os demais pacientes com creatinina ≤ 1,5mg/dL.**

Descritores: **Revascularização Miocárdica. Mortalidade Hospitalar. Insuficiência Renal Crônica. Fatores de Risco. Creatinina.**

INTRODUCTION

Kidney failure is one of the most important risk factors for complications after both acute ischemic cardiac events [1-4] and in cardiac surgery, causing longer hospital stays and higher in-hospital mortality [5,6]. In coronary artery bypass grafting (CABG), the previous presence of renal dysfunction is an independent predictor of operative mortality [5.7 to 12].

Plasma creatinine (PCr) alone is not sufficiently precise to identify renal dysfunction - in large population samples, up to 17% of patients with “normal” PCr show significant impairment of renal function [6,13-15].

The measurement of glomerular filtration rate (GFR) by 24-hour endogenous creatinine clearance (eCrCl) provides accurate and useful results in the evaluation of renal function in clinical practice. However, this method requires an extended period of time for obtaining the urine and is also subject to errors such as those arising from incomplete collection of urine in the period. Thus, some equations were developed to estimate creatinine clearance using only the values †of PCr, body weight, age and gender [5,13,16-20]. Because of its simplicity, one of the most widely used equations is that proposed by Cockcroft & Gault (CG) [21]. Corrections for obesity or overweight were developed for this formula, in order to minimize the overestimation of CrCl [22], but these calculations are often not normally used.

The main objective of this study was to compare patients with PCr d” 1.5 mg/dL (133 micromol/L) who had undergone CABG, distributing them into two groups according to estimated creatinine clearance, normal or reduced, and finding differences rates of in-hospital mortality, total hospital length of stay (THLS) and postoperative hospital stay (POHS). Secondly, we also compared these findings with those of other patients (reduced CrCl and PCr > 1.5 mg / dL).

METHODS

This is a historical cohort study. All patients undergoing CABG between January 1996 and June 2004, at the Institute of Cardiology of Rio Grande do Sul were assessed for inclusion. Surgery without cardiopulmonary bypass and other surgical procedure simultaneous with CABG (such as valve surgery, aneurism repair, ventricular repair, carotid endarterectomy) were considered exclusion criteria. Pre-, intra- and postoperative data were collected from medical records of each patient using a standardized protocol. Quality control of collected data was performed on random samples of records for each month of all nine years included in the study.

MÉTODOS

Data related to several variables were recorded, such as gender, age, weight, height, PCr, dates of hospitalization, surgery and hospital discharge (allowing to establish the total length of hospital stay [TLHS] - from admission until hospital discharge; time and postoperative hospital stay [POHS] - surgery until hospital discharge). Mortality (all cause) was considered as the one during the hospitalization. PCr was measured by the same method and same laboratory. In case of more than one measure of PCr to the same patient, it was considered the last value before surgery. As the CrCl

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estimated by CG equation ($CrCl_{GG}$) does not consider any correction for body surface area (BSA) standard of 1.73 m^2, the following calculation was included in our formula: [CrCl/m^2 = 1.73 (mL/min/1.73 m^2): ((140 - age (years)) × weight (kg))/(72 × CPR (mg/dL)) x (1.73 (m^2)/SC (m^2)) (0.85 if female)]. And as $CrCl_{GG}$ overestimates GFR in patients with overweight or obese, the correction formula proposed by Saracino et al. [22] was applied to those with body mass index (BMI) greater than 25 kg/m2 - CrCl x (1.25 – {0.012 x BMI}). The BSA was calculated using the formula of Dubois - [BS (m^2) = 0.007184 × height (cm) 0725 × weight (kg) 0425] [23]. The end result of all these calculations was called CrCle / 1.73 m^2.

Patients with PCr ≤ 1.5 mg/dL were divided into two groups: eCrCl/1.73 m^2 ≥ 60 mL/min - normal renal function Group A - or <60 mL/min - reduced kidney function, Group B (according to the classification of chronic kidney disease stage 3 of the National Kidney Foundation [24]). All other patients had PCr> 1.5 mg/dL and eCrCl/ 1.73 m2 <60 mL / min (Group C).

A ROC curve for each gender was designed to establish the cutoff value of PCr required to detect an eCrCl/1.73 m^2<60 mL/min. Another ROC curve was established to compare PCr and eCrCl/1.73 m^2 in order to predict mortality. A dispersion graph was created with all values † eCrCl/ 1.73 m^2 with their respective values †of PCr. Statistical analysis was performed with SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Tukey test was used for paired comparisons of data between the three different groups.

The study was approved by the Research Ethics Committee of the Institute of Cardiology of Rio Grande do Sul and by the Research Ethics Committee of Lutheran University of Brazil.

RESULTS

In the 102 months of analysis, 4,765 patients had undergone CABG with cardiopulmonary bypass, of whom 4688 (98.4%) had all the necessary data for calculating the eCrCl/1.73 m^2.

Age (mean ± SD) of the study population was 61.2 ± 10.1 years, with a prevalence of 71.5% males. Table 1 shows the main characteristics of all patients in each group.

Among patients with PCr ≤ 1.5 mg/dL, the prevalence of eCrCl/1.73 m2 < 60mL/min was 27.8%.

Maximum PCr of 1.5 mg/dL as the cutoff point had a sensitivity of 18.9% and a specificity of 100% to detect a eCrCl/1.73 m2 <60 mL/min, with a negative predictive value of 72.2 % and a positive predictive value of 100%. Table 2 and Figures 1 and 2 show the coordinates of sensitivity and specificity of the ROC curve for PCr values †to detect eCrCl/1.73 m2 <60 mL/min for both genders.

A graph of dispersion (Figure 3) was established in order to visually demonstrate the possible values †of eCrCl/1.73 m2 for the same value of PCr.

Table 1. Clinical and laboratory data of patients.

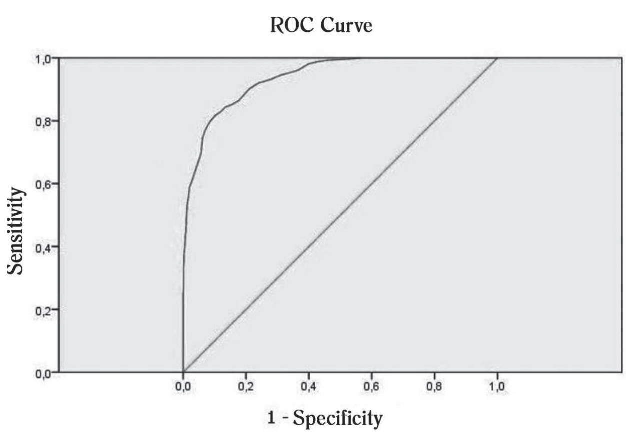
Group	All	A	B	C
Patients – n (%)	4.688(100%)	3.177(67.8)	1.226(26.2)	285(6.1)
Age (years)	61.2 ±10.1	57.6±9.1	69.2 ±7.3	66.5 ±9.1
Gender (%) - female	28.5	25	39.2	21.8
Body surface (m^2)	1.82 ± 0.18	1.84 ± 0.19[a]	1.77 ± 0.18[b]	1.83 ± 0.17[a]
BodyMass Index > 25 kg/m^2 (%)	71.6	64.3	69.8	69.6
BodyMass Index (kg/m^2)	27.4 ± 4.0	27.6 ± 3.9	26.8 ± 4.0	27.3 ± 4.1
eCrCl (mL/min/1,73m^2)	69.9 ±20.2	80.2 ±15.3[a]	51.4±6.2[b]	34.8 ±8.8[c]
Serum Creatinine (mg/dL)	1.05 ± 0.37	0.92 ± 0.16[c]	1.18 ± 0.17[b]	2.00 ± 0.84[a]
Hemoglobin (g/dL)	13.0 ± 1.6	13.3 ± 1.5[a]	12.5 ± 1.5[b]	12.1 ± 1.6[c]
Hematocrit (%)	39.8 ± 4.7	40.5 ± 4.5[a]	38.4 ± 4.5[b]	37.3 ± 5.8[c]
Glucose (mg/dL)	120.8±47.2	120.7±47.0[a]	120.8 ±46.4[a]	122.4 ±52.9[a]
Pump surgical time (min)	79.8 ± 24.6	78.5 ±24.0[b]	81.4 ±25.1[b]	86.8 ±27.4[a]
Ischemia time (min)	48.4 ±15.7	48.0 ±15.6[b]	49.1± 15.8[ab]	50.4 ±16.8[a]
Left ventricular function preoperatively (ejection fraction in %)	67.5 ± 16.6	68.2 ± 16.1	67.3 ± 17.0	61.1 ± 19.5
Urgent surgical criteria (%)	14.7	13.1	17.0	22.7
Emergency surgical criteria (%)	2.7	2.4	3.1	4.3
Hypertension (%)	61.4	58.3	67.1	71.2
Diabetes (%)	28.8	27.6	30.6	35.1
Peripheral vascular disease (%)	12.7	10.3	17.2	20.4
Cerebrovascular disease (%)	8.2	6.4	10.1	19.3
Use of intravenous radiocontrast up to 10 days before the surgery - n (%)	1.875(40.0)	1.239(39.0)	519(42.3)	117(41.1)

Data expressed as mean ± standard deviation, unless otherwise specified.
*Values with different letters in superscript represent significant differences according to Tukey's test (*P *<0.05)*

Table 2. Sensitivity and specificity (%) of serum creatinine to detect eCrCl < 60mL/min/1.73m²

	Creatinine	Sensitivity	Specificity
Men	0.90	99.6	35.2
	1.00	94.5	63.0
	1.11	86.0	85.9
	1.20	69.5	95.4
	1.30	48.3	98.8
Women	0.70	100	24.6
	0.80	99.3	54.0
	0.91	85.0	84.4
	1.00	63.5	96.3
	1.10	40.2	99.5

Values obtained from the coordinates of the ROC curve



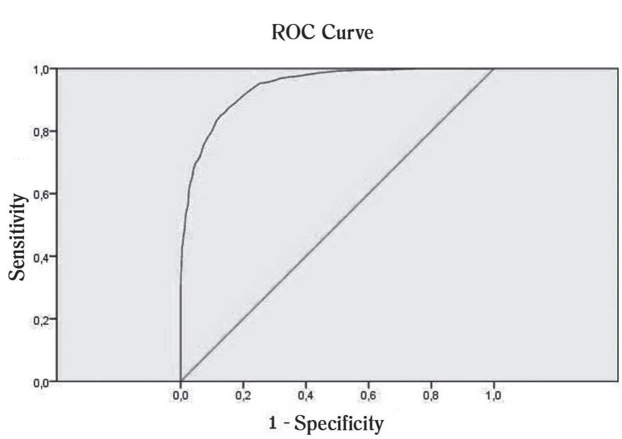


Fig. 1 and 2 - Coordinates of sensitivity and specificity on the ROC curve for PCr values for eCrCl/1.73 m² <60 mL/min for both genders

Total length of hospital stay (TLHS) and length of postoperative hospital stay (POHS)

Patients in groups B and C had TLHS and POHS significantly higher than group A (*P* <0.05, Tukey test) - Figure 4.

In-hospital mortality

The rates of in-hospital mortality (from any cause) in groups A and B were 2.8% and 5.8% respectively, while in group C was 11.6%.

Group B patients had a relative risk (RR) of in-hospital mortality of 2.09 (CI95% :1,54-2, 84) compared to group A, while those in group C had an RR of 4, 18 compared to group A (CI95%: 2.86 to 6.12) - Figure 5.

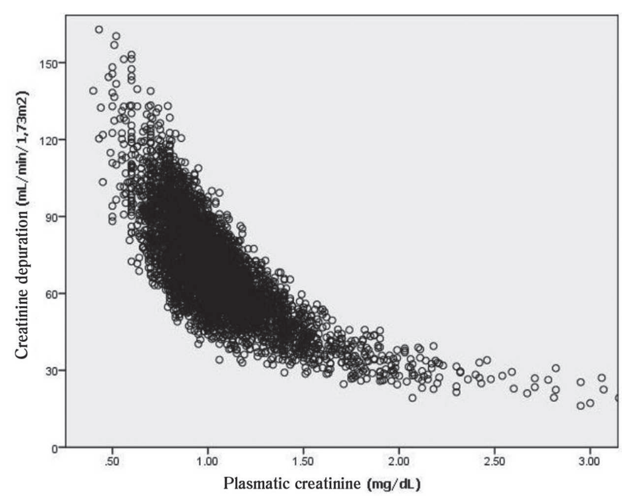


Fig. 3 - Dispersion graph with possible values of eCrCl/1.73 m² for the same value of PCr

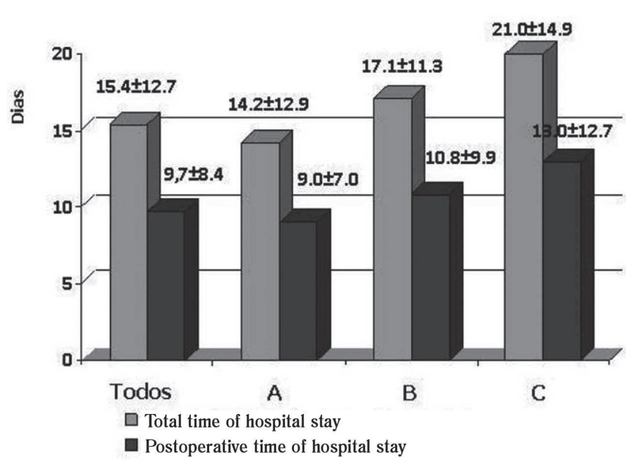


Fig. 4 - Patients in groups B and C had TLHS and POHS significantly higher than group A.
P <0.05, Tukey test

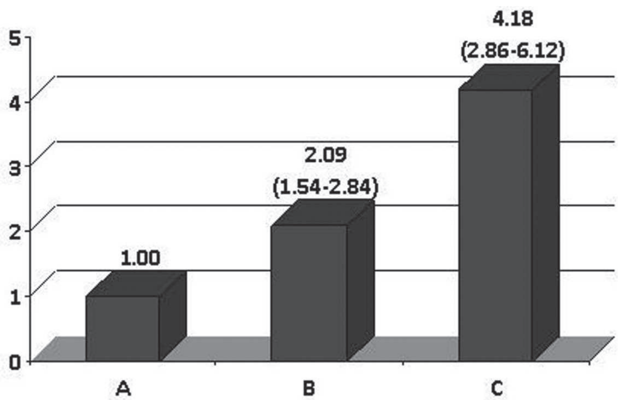


Fig. 5 - Patients in group B had a relative risk (RR) of in-hospital mortality of 2.09 (CI95% :1.54-2.84) compared to group A. The C group had a RR of 4.18 compared to group A (CI95%: 2.86 to 6.12)

DISCUSSION

The study included all patients undergoing CABG with cardiopulmonary bypass regardless of the criterion for elective, urgent or emergency, and the rate of in-hospital mortality was 4.1%. This finding is similar to those obtained by Roques et al. [25] and Vogt et al. [26]. Roques et al. [25], whose database was also used to develop the EuroSCORE and included 19,030 patients from 128 surgical centers in Europe, found overall in-hospital mortality of 4.8%. And Vogt et al. [26], when studied data from 10,000 consecutive patients from 81 cardiac surgery centers in Germany, found a mortality rate of 3.91% in 30 days postoperatively.

Our data showed a significant increase in TLHS and POHS related to the finding of reduced renal function (Figure 4), as previously observed by Witczak et al. [8], when studying patients with chronic renal failure undergoing major cardiovascular surgical procedures. Our patients with PCr ≤ 1.5 mg/dL, but with eCrCl/1.73 m^2 <60 mL/min (Group B) had significantly higher TLHS (2.9 days longer) and POHS (1.8 more days) than those in Group A. Comparing the group C (those with arguably compromised kidney function) with group A, we find even greater increase of TLHS and POHS (6.7 and 4.1 days longer, respectively).

Duncan et al. [14] used the CG equation to estimate the CrCl in the general population of 2781 patients who had PCr determined for clinical purposes and found that 14% of patients could be defined as belonging to what we consider group B. In our study, we found similar results using the equation CG alone. However, after adjusting for body surface area of †1.73 m2 and applying the Saracino formula for overweight and obesity, the prevalence of patients with PCr ≤ 1.5 mg/dl and with impaired renal function increased to 27.8%.

In a previous study of 1,495 patients in our city, Burmeister et al. [15] tested the sensitivity and specificity of a PCr of 1.2 mg/dL to detect an eCrCl <60 mL/min through the CG equation and obtained 49.1% and 95.2%, respectively. With a cutoff point of PCr 1.5 mg/dL, sensitivity of 18.9% and a specificity of 100%. Therefore, a patient with PCr above 1.5 mg/dL certainly has kidney failure, although we can not rule out some degree of renal dysfunction when the creatinine is equal to or less than 1.5 mg / dL due to its low sensitivity. And while values †greater than 1.2 mg/dL are suggestive of renal dysfunction, such values are unable to fully confirm or rule out this hypothesis. In our study, evaluating the coordinates of the ROC curve constructed to detect an e CrCl <60mL/min by PCr, we found that a properly balanced cutoff would be 0.91 mg/dL (sensitivity = 85.2% and specificity = 84.4%) for women and 1.11 mg/dL (sensitivity = 86.0% and specificity 85.9%) for men.

Wijeysundera et al. [13] presented a graph in which the dispersion of the CrCl for the values †of PCr was higher than in our chart (Figure 3), which is certainly due to the fact that they considered the CG equation alone, without adjustment for surface body or for overweight or obesity. We can also observe patients already presenting a CrCl less than 60 mL/min with a PCr of 0.79 mg/dL, a value that, without the use of a formula for estimating the CrCl would be considered normal. Moreover, it is remarkable that in the case of any cutoff point for a lower PCr detecting a compromised CrCl, more patients with normal renal function would be considered as having renal dysfunction.

Cooper et al. [9] in a recent study by the Society of Thoracic Surgeons, and Holzmann et al. [18], with data from a Swedish hospital, showed an increased odds ratio for mortality among patients with mild renal insufficiency (30-59 mL/min) of 1.55 and 1.3, respectively, and in patients with severe renal insufficiency (<30 mL/min) of 2.87 and 2.8 in each study, respectively. Among our patients, group B, with an average of CrCl 51.4 mL/min, and group C with 34.8 mL/min, showed a RR of 2.1 (95% CI: 1.5 to 2.8) and 4.18 (95% CI: 2.9 to 6.1) compared to group A (mean CrCl = 80.2 mL/min). Pimenta et al. [5] in a retrospective analysis of in-hospital outcome of renal function in 274 patients, also demonstrated a higher rate of mortality among those with lower values †of CrCl.

For our patients, the area under the ROC curve for CrCl and PCr for predicting mortality was 0.664 and 0.595, respectively, comparable to what was found by Holzmann et al. [18] (0.71 and 0.62). These data show that CrCl is better than PCr in predicting hospital mortality.

Our study may have had some limitations, as it has been performed with patients from a single hospital, which restricts the applicability of its results to other similar centers. Group A also tended to lower average age, lower levels of criteria for emergency care and a lower prevalence of cerebrovascular disease, which could represent biases. Moreover, our calculations of RR were not adjusted for potential confounding factors. Also we did not discriminate against those who needed dialysis in the postoperative period, in addition, some factors may have affected the measurement of PCr as the use of diuretics, nephrotoxic drugs such as antibiotics, intravenous radiocontrast, or heart failure.

On the other hand, our study assumes importance due to the significantly increased size of the sample and the fact that our results were comparable to other similar studies. In addition, the Institute of Cardiology of Rio Grande do Sul is one of the most important reference in cardiovascular surgery in southern Brazil.

In conclusion, this cohort of patients undergoing CABG alone, over one quarter of those with PCr less than 1.5 mg/dL had significant loss of kidney function - CrCl below 60 mL/min. This substantial group of patients, whose renal dysfunction would have not be detected if we had take into account only the parameter of the “normal” PCr, presented twice as much risk of mortality as the TLHS and POHS in relation to other patients with PCr ≤ 1,5mg/dL.

Therefore, we strongly recommend that patients with indication for CABG have their CrCl estimated even when the result of the PCr is within normal values, in order to identify hidden renal disease from any cause and alert to this powerful risk factor.

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