

CLINICAL STUDY

Does Urinalysis Predict Acute Renal Failure After Heart Surgery?

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ABSTRACT

Acute renal failure (ARF) usually develops in 5% to 30% of patients undergoing heart surgery and is associated with a more complicated clinical evolution course and with an excessive mortality of up to 80%. The objective of this study was to verify the frequency of ARF in postoperative coronary artery bypass surgery with and without cardiopulmonary bypass, by the evaluation of renal function markers' performance [plasma creatinine, plasma urea, urinalysis, fractional excretion of sodium, creatinine clearance and Alpha-glutathione S-transferase (α -GST)], besides to verify possible relations between clinical variables involved in postoperative heart surgery and the occurrence of renal insufficiency.

Key Words: Acute renal failure (ARF); Heart surgery; Postoperative; Renal function marker; Alpha-glutathione S-transferase (α -GST).

INTRODUCTION

Classically, acute renal failure (ARF) is a syndrome characterized by a rapid decline of glomerular filtration rate and retention of nitrogenated products such as urea and creatinine.^[1] In general, ARF occurring after coronary artery bypass surgery (CABG) results from marked renal ischemia secondary to hypotension and to low cardiac output.^[2]

According to Levy et al.,^[3] Star^[4] and Zanardo et al.,^[5] ARF develops in 5% to 30% of the patients submitted to heart surgery and it has been convincingly shown that renal dysfunction is associated with a more complicated clinical course and with mortality of up to 80%. However, according to Sural et al.,^[6] within the surgical context, approximately 18% to 47% of cases develop ARF, with a mortality rate ranging from 40% to 100%.

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Evaluation of patients with ARF of any origin requires a detailed clinical history, physical examination and urinalysis, previous records, the determination of drugs under use, laboratory tests, imaging exams, and, occasionally, a renal biopsy.^[1] Rigorous biochemical criteria should be established for the screening of these patients since a delayed intervention and diagnosis can be considered factors of extreme relevance in terms of dialysis outcome or mortality.

Recent studies have suggested the use of specific urinary enzymes to demonstrate the site of renal insult in order to facilitate intervention and patient treatment. These are enzymes that are naturally eliminated during renal lesion, such as *N*-acetyl-beta-D-glucosaminidase, β_2 microglobulin, alanine-aminopeptidase and α -glutathione S-transferase (α -GST).^[7]

GSTs are a group of enzymes found in high concentrations in renal tubule cells. Several isoforms are known, each differing in distribution along the nephron.^[8] In humans, α -glutathione S-transferase (α -GST) are only found in proximal tubules and are readily eliminated into urine or extracellular fluid in events of proximal tubular damage, representing sensitive biomarkers specific for acute renal effects. A notable difference between urinary α -GST and most other markers of renal damage is that α -GST is derived from the cytosol of renal tubular cells, a fact that confirms its origin and its specificity for the proximal tubular region (S3).^[9,10] GST, by being undetectable under normal conditions, has an advantage over the remaining enzymes that can be detected under basal conditions in the absence of damage.^[8]

In view of the difficulty in the early identification of ARF, especially in patients submitted to CABG, and of the multiple clinical variables involved in this event, reconfirming the severity of this complication, one of the objectives of the present study was to assess the performance of the main clinical measures routinely adopted and of urinary α -GST in terms of the prediction and diagnosis of postoperative ARF.

OBJECTIVES

To determine the frequency of ARF in patients submitted to CABG with cardiopulmonary bypass (CPB) and without CPB.

To analyze the performance of the markers of renal function and their predictive and diagnostic characteristics for ARF in the sample studied.

METHOD AND SERIES

This was a prospective longitudinal study with a quantitative approach.

The study was conducted in the Admission and Cardiac Recovery units of a teaching, research and assistance institution of a public hospital in the State of São Paulo specializing in Cardiology.

The study sample consisted of 41 patients submitted to CABG, with and without CPB, on an exclusively elective basis in the above service. The Ethics Committee of the hospital in question approved the protocol. All patients signed a Free and Informed Consent form.

Patients were sampled on the basis of the following exclusion criteria: oliguria (a urinary flow of less than 400 mL/day); previous history of ARF; plasma creatinine levels higher than 1.4 mg/dL over a period of 24 hours before surgery; age of less than 13 years or more than 65 years; in use of an intra-aortic balloon or other devices for circulatory assistance during the postoperative period; total intraoperative circulatory arrest. These criteria were selected in order to exclude patients with signs of previous renal damage or with some treatment interference from the study, which could be considered to be a cause of ARF other than CABG or the use of an extracorporeal procedure.

All patients included in the study were monitored during the perioperative period (preoperative period and 24 and 72 hours after surgery) to obtain clinical and laboratory data: patient identification; base diseases; medications in use preoperatively; application of contrast; laboratory results; type and duration of surgery and duration of CPB; body temperature; bleeding; urinary flow; ventilation; pulse oximetry; use of drugs and laboratory tests.

The laboratory data used as markers of renal function were: plasma creatinine, creatinine clearance, measurement of urinary sediment, fractional excretion of sodium (FE_{Na}), and quantification of the excretion/concentration of urinary α -GST, in addition to plasma sodium, potassium and urea. To obtain these laboratory values, each patient was submitted to preoperative analysis of renal function. Data concerning the history and clinical course of each patient were obtained from the medical records.

ARF was defined as an abrupt decline in renal function occurring up to 72 hours after CABG, represented by the reduction in creatinine clearance to rates of less than 75 mL/min. It should be pointed out that the normal value of creatinine clearance is variable, but should always be about 75 to 125 mL/min.

Thus, creatinine clearance was used as the gold standard and all the factors studied were compared to it.

Urinary α -GST

Urinary α -GST is a highly sensitive enzyme specific for renal damage whose levels increase under conditions of damage to the proximal tubular cells.^[10]

The exam consists of the detection of this protein with a specific antibody by enzyme-linked immunosorbent assay (ELISA). All patients were tested for urinary α -GST during the preoperative period and 24 hours after surgery and significant changes in its levels were interpreted as damage to the proximal tubules.

α -GST excretion/concentration was determined according to the following formula, as indicated by the manufacturer of the kit:

$$\text{ng}\alpha\text{GST}/\text{min} = [\alpha\text{GST}]\mu\text{g}/\text{L} \cdot \text{V}/\text{T}$$

where: V=total urine volume in mL, T=T₂-T₁ (in minutes), T₂=time of urination, T₁=time of the previous urination.

Postoperative data concerning plasma creatinine, creatinine clearance, urinary sediment, FE_{Na} and urinary α -GST were obtained 24 hours after the end of heart surgery (CABG) and were compared to preoperative results in order to assess the performance of α -GST as a marker for the prediction of ARF in relation to the other parameters.

A receiver operator characteristic (ROC) curve was constructed to confirm the relation between the sensitivity and specificity of urinary α -GST. The ROC curve for α -GST was used for a decision about the best cut-off point, i.e., the reference value for this variable.

Renal function was monitored up to 72 hours after surgery. Only plasma creatinine, creatinine clearance, urinary sediment and FE_{Na} were determined. α -GST was not determined at the 72-hour time point because the expectation was that it would be an early predictor of ARF.

All renal function data obtained before and after CABG were later compared to assess the frequency of ARF and to identify the best predictive and diagnostic factors for its occurrence.

Statistical Analysis

Continuous data were first categorized using the cut-off values adopted at the Institution where the research was carried out. The Pearson Chi-square test was used for the analysis of categorical variables. The data were expressed as absolute (n) and relative (%) frequency. Analysis of the continuous variables was performed by using Mann-Whitney test for nonparametric continuous variables (data were expressed as median and 25th and 75th percentile) and Student's *t*-test for parametric continuous variables using Welch correction when appropriate. Adherence of the data to the normal curve was defined by the K-S distance test.

Table 1. Data concerning the frequency of the use of medications before and after surgery and the postoperative occurrence of ARF.

Medications	ARF (n=20)					
	Before surgery			After surgery		
	n	%	p	n	%	p
Ca channel blocker	3	15.0	0.477	9	45.0	0.636
ACEI	15	75.0	0.228	6	30.0	0.032
Beta blocker	18	90.0	0.240	2	10.0	0.520
Anti-platelet aggregation agent	19	95.0	0.972			
Thiazide diuretic	2	10.0	0.520			
Uricosuric agent	5	25.0	0.014			
Hipolipemic agent	12	60.0	0.440			
Nitrate	12	60.0	0.427	10	50.0	0.443
Hipoglycemic agent	1	5.0	0.010	2	10.0	0.240
NHAI	2	10.0	0.137	0	0.0	0.323
Inotropic agent				15	75.0	0.796

p<0.05.

NHAI (nonhormonal antiinflammatory agent).

InCor. Sao Paulo, 2002.

Table 2. Results concerning the occurrence of ARF and its relation to the frequency of alteration of biochemical parameters determined before surgery (pre) and 24 and 72 hours after surgery.

Parameters	With ARF (n=20)					
	pre		24 h		72 h	
	%	p	%	p	%	p
Plasma Na (mEq/L)	10.0	0.675	30.0	0.655	5.0	0.614
Plasma K (mEq/L)	0.0	0.367	5.0	0.582	5.0	0.972
Plasma urea (mg/dL)	45.0	0.031	35.0	0.123	30.0	0.414
Plasma Cr (mg/dL)	0.0	0.876	5.0	0.972	5.0	0.300
Urinary Cr (g/24 h)	35.0	0.532	55.0	0.273	50.0	0.008
24 h Cr clearance (mL/min)	70.0	0.493	80.0	0.049		
FE _{Na} (%)	15.0	0.948	50.0	0.647	90.0	0.004
Urinary sediment:						
Leukocytes (/mL)	30.0	0.819	45.0	0.636	35.0	0.910
Hemoglobin	25.0	0.067	75.0	0.796	40.0	0.427
Epithelial cells (/mL)	15.0	0.294	5.0	0.578	10.0	0.240
Casts (/mL)	25.0	0.067	25.0	0.796	15.0	0.731
Crystals	5.0	0.169	10.0	0.675	5.0	0.317
Bilirubin	0.0	0.876	0.0	0.876	5.0	0.972

p<0.05.

Cr (creatinine).

InCor. Sao Paulo, 2002.

p values below 0.05 were considered statistically significant. For α -GST, the specificity and sensitivity test were also performed.

angiotensin converting enzyme inhibitors (ACEIs) taken postoperatively ($p=0.032$) (diagnostic factor).

The data demonstrate that factors such as the interval between the use of contrast and surgery, surgical duration, CPB duration and immediate postoperative

RESULTS

The results obtained in the present study refer to a sample of 41 patients (29 males, 71%, and 12 females, 29%) who were followed from the preoperative period to 72 hours after CABG with and without CPB. Mean (\pm SD) age was 56.3 ± 7.7 years, mean BMI was 27.0 ± 4.1 kg/m², mean weight was 72.9 ± 13.3 kg, and mean height was 1.64 ± 0.10 m.

After CABG, 20 patients (48.8%) developed ARF and 21 (51.2%) did not. ARF preferentially occurred in patients with a mean age of 60 years, whereas younger patients (53 years on average) did not develop ARF after surgery ($p=0.004$).

There was no significant prevalence of any disease as the cause of ARF.

Table 1 shows that among the medications used by the patients during the perioperative period, those correlated with the occurrence of ARF were only the uricosuric agent ($p=0.014$) and the hypoglycemic agent (0.010) taken preoperatively (predictive factor) and the

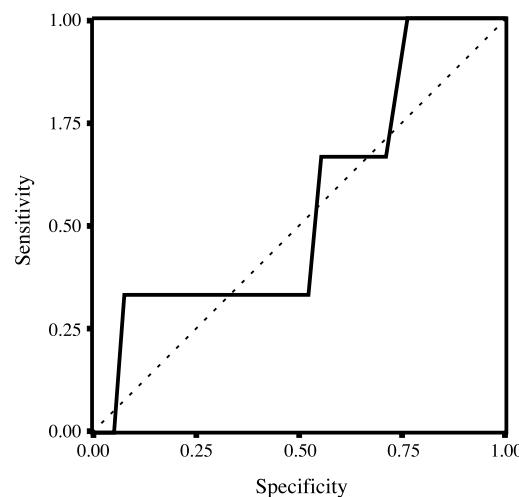


Figure 1. ROC curve for the evaluation of the performance of urinary α -GST in relation to ARF during the preoperative period. InCor. Sao Paulo, 2002.

Table 3. Results concerning urinary α -GST related to the type of surgical technique adopted (with and without CPB) and to the occurrence of ARF after CABG, using the Mann-Whitney test.

	α -GST (n=41)	
	Median (25%–75%)	<i>p</i>
Surgical technique		
With ECC	2.600 (1.450–12.375)	0.023
Without ECC	1.000 (0.700–2.800)	
ARF		
Present	1.600 (0.900–9.675)	0.548
Absent	2.100 (1.150–9.050)	

p<0.05.

ECC (extracorporeal circulation).

InCor. Sao Paulo, 2002.

aspects such as water balance, duration of mechanical ventilation, body temperature, bleeding, and pulse oximetry did not confirm a risk for postoperative ARF in the study sample.

The postoperative occurrence of ARF was not associated with the use (n=26) or not (n=15) of CPB (*p*=0.275), although 11 patients in the group with ARF had been submitted to CABG with CPB.

The type of surgery performed did not interfere with the postoperative occurrence of ARF (*p*=0.93).

Statistical analysis of all the biochemical parameters for the sample carried out in order to determine their significance as predictive (pre- and 24 hours) and diagnostic (72 hours) factors for ARF yielded the results presented in Table 2. The table shows that parameters such as plasma sodium and potassium were not relevant for the prediction or diagnosis of ARF, whereas plasma urea was statistically significant as predictor of ARF during the preoperative period and creatinine clearance during the first 24 hours after surgery. Urinary creatinine and FE_{Na} were significant diagnostic factors, whereas urinary sediment was significant neither as a predictive nor as a diagnostic factor for ARF.

Figure 1 shows that the curve does not have an area of more than 0.8 and therefore it was not suitable to be treated categorically. In a continuous mode using absolute values, the Mann-Whitney test was significant.

The data in Table 3 show that there was an association between the surgical technique used (with and without CPB) and urinary α -GST during the postoperative period, i.e., the patients submitted to CABG with CPB had a greater alteration in urinary α -GST than those submitted to CABG without CPB. However, there was no association between α -GST and the occurrence of ARF during the postoperative period.

DISCUSSION

The present patient sample was characterized by a prevalence of males, who are known to have a higher rate of obstructive coronary disease.^[11] Age (60 years on average) proved to be a predictive factor for the occurrence of ARF. Although there is no consensus in the literature,^[5,12,13] Brady et al.,^[1] Suen et al.,^[14] and Mangano et al.^[15] have stated that advanced age represents a risk factor during the preoperative period.

In the present study, a high frequency of ARF (48.8%) was detected after CABG, in agreement with data reported by Hou et al.^[16] and Turney et al.,^[17] who stated that surgical procedures are responsible for 18% to 47% of all cases of ARF.

With respect to base diseases, although some showed high prevalence, such as hypertension, dyslipidemia and diabetes, no relationship between them and the occurrence of ARF was observed in contrast to previously reported data.^[12,13,18,19]

The present study also showed that variables such as the contrast–surgery interval, surgical duration, water balance and duration of mechanical ventilation in the perioperative period were not related to the occurrence of ARF, even though previous reports^[20] have emphasized that the duration of aorta clamping and the total duration of surgery are significantly correlated with postoperative ARF.

In addition, no significant correlation was detected between combined surgical procedures (i.e., CABG and other surgeries such as fasciotomy or thrombectomy, except for CABG associated with a valve exchange) or between CABG alone and the occurrence of postoperative ARF. This finding contradicts previous reports, which attributed a relevant risk for ARF to combined surgeries.^[1,13,21] It should be pointed out, however,

that these data refer to CABG combined with valve exchange, a fact that definitely represents a greater surgical risk.

The present study also demonstrated no association between the surgical technique adopted (with and without CPB) and the occurrence of ARF. Literature data, however, are inconclusive about a possible relationship.^[22-28] Probably other factors like preoperative renal function are more important to determine the occurrence of ARF after surgery,^[29] which reinforce the importance of the preoperative evaluation including renal function.

Because of the considerable difficulty involved in the early detection of ARF, a set of markers of renal damage ranging from those classically used to the enzymes considered to be ideal biomarkers for the early detection of renal insult, such as α -GST, was adopted.

It was observed that the measurement of creatinine clearance was a good predictor of renal damage after CABG. Differently, plasma creatinine was not a good predictive or diagnostic factor for renal damage. This was probably due to its variability according to body mass, patient age, degree of hydration, and use of given medications that might have interfered with the result, mimicking a situation of ARF.^[30-32]

Among the factors considered to be diagnostic, those that confirmed ARF were fractional excretion of sodium and urinary creatinine, proving to be significant during the first 72 hours after surgery. FE_{Na} is the most accurate index for the distinction between the two major causes of prerenal ARF and acute tubular necrosis (ATN).^[33]

Fifty percent of the patients presented urinary creatinine values below reference levels. This usually occurs when there is tubular damage and the mechanisms of solute reabsorption by the renal tubules are impaired, with the consequent occurrence of oliguria.^[34] Despite this the marker did not confirm to be a predictor, this finding should be also taken into consideration in the preoperative renal evaluation.

On the other hand, the urinary sediment did not show a significant result for the occurrence of ARF. According to Riella,^[35] the urinary sediment may indicate the presence of nephropathy and often the nature and extent of the lesions, although it does not give an idea of renal function when considered separately.

Urinary α -GST, which in humans represents a highly specific and precise enzyme indicating proximal tubular damage, is promptly released into urine after the occurrence of damage, such as ischemic lesion. In the present study, no relation was detected between this enzyme and the occurrence of ARF during the preoperative ($p=0.566$) and postoperative period

($p=0.548$). However, a correlation was observed between α -GST and the surgical technique (with and without CPB) ($p=0.023$), a fact that, considered separately, may indicate tubular suffering due to an inflammatory mechanism induced by the use of the extracorporeal system and not yet reproduced by significant changes in creatinine clearance.^[36-38]

In summary, the present study confirmed a prevalence of the male sex for CABG and that ARF after this surgery was significantly related to the age, preferentially occurring in individuals older than 60 years. Factors such as the use of uricosuric and hypoglycemic agents were significantly associated with the occurrence of ARF during the preoperative period and the use of ACEIs during the postoperative period. The major markers of function for ARF were creatinine clearance, plasma urea, FE_{Na} and urinary creatinine. The use of CPB was not related to the occurrence of ARF.

These findings emphasize the need to establish a judicious protocol for the evaluation of renal function starting during the preoperative period and for the evaluation of individual factors such as age and drug use in order to guarantee the preservation of postoperative renal function. It is important to define a clinical profile for ARF and for the protective measures involved in this situation in order to favor the adoption of timely multidisciplinary conducts that will prevent the actual installation of ARF.

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