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Preoperative risk factors for the development of acute renal failure in cardiac surgery

Fatores de risco pré-operatórios para o desenvolvimento de insuficiência renal aguda em cirurgia cardíaca

Ana Claudia KOCHI[1], Antonio Sérgio MARTINS[2], André Luís BALBI[3], Marcos Augusto de MORAES E SILVA[4], Maria Cristina Pereira LIMA[5], Luís Cuadrado MARTIN[3], Rubens Ramos de ANDRADE[2]

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Resumo

Objetivo: **Avaliar os fatores de risco clínicos pré-cirurgicos para o desenvolvimento de Insuficiência Renal Aguda (IRA) em pacientes submetidos à cirurgia cardíaca.**

Método: **Foram estudados, de modo prospectivo, 150 pacientes submetidos à cirurgia cardíaca, durante 21 meses consecutivos, havendo um leve predomínio de homens (57%), idade média de 56 ± 15 anos, sendo que 66% apresentavam insuficiência coronariana como principal diagnóstico e 34% valvulopatias. A mediana da creatinina sérica no período pré-operatório foi de 1,1 mg/dl. IRA foi definida como elevação de 30% da creatinina sérica basal. O protocolo de variáveis clínicas teve seu preenchimento iniciado 48 horas antes do procedimento cirúrgico e encerrado 48 horas após o mesmo, incluindo variáveis cardiológicas e não-cardiológicas, além de resultados laboratoriais.**

Resultados: **A IRA esteve presente em 34% dos casos. Após análise multivariada, presença de doença vascular periférica foi fator pré-operatório identificado.**

Conclusão: **Os resultados obtidos nesse estudo permitiram sinalizar alguns fatores contributivos para o desenvolvimento de IRA em cirurgia cardíaca, o que pode possibilitar condutas clínicas simples para evitar a disfunção renal nestas situações e, conseqüentemente, redução da taxa de mortalidade. No presente trabalho, o tamanho da amostra talvez tenha impedido a identificação de outros fatores de risco significativos.**

Descritores: **Insuficiência renal aguda. Procedimentos cirúrgicos cardíacos. Complicações pós-operatórias.**

1. M.Sc; Physician
2. PhD; Professor Cardiovascular Surgery Department of HC-UNESP.
3. PhD; Physician of the Nephrology Department of HC-UNESP.
4. Livre docente; Head of Cardiovascular surgery Department of HC-UNESP.
5. PhD; Professor of the Psychiatry Department of HC-UNESP

Work carried out in the Medical School of HC-UNESP, Botucatu, SP.

Correspondence address
Ana Claudia Kochi. Disciplina de Cirurgia Cardiovascular do Departamento de Cirurgia e Ortopedia da Faculdade de Medicina de Botucatu-UNESP (ANEXO D) CEP: 18618-970. Distrito de Rubião Junior, Botucatu, SP. Tel: (14) 3814-2068/(14) 9775-0219. Fax: (14) 3815-7615.
E-mail: kochi@fmb.unesp.br

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Abstract

Objective: **To evaluate clinical risk factors for the development of Acute Renal Failure (ARF) in patients who undergo cardiac surgery.**

Method: **Over a period of 21 consecutive months, one hundred and fifty patients who underwent cardiac surgery were studied. There was a slight prevalence of men (57%) and the average age was 56 ± 14.8 years. Sixty-six percent presented with coronary artery disease as the main diagnosis and 34% valvular heart disease. The median preoperative serum creatinine was 1.1 mg/dL. ARF was defined as a 30% increase in serum creatinine above baseline. The protocol of clinical variables initiated 48 hours before the surgical procedure and finished 48 hours after it and included cardiological and non-cardiological variables and laboratory data.**

Results: **ARF was present in 34% of the cases. After multivariate analysis, being a man and the presence of peripheral vascular disease were identified as the preoperative factors.**

Conclusion: **The results obtained in this study identified some risk factors for the development of ARF in cardiac surgery, suggesting simple clinical procedures that may prevent renal dysfunction in these situations and, consequently, reduce the mortality rate. In the present study, the sample size has possibly impeded the identification of other significant risk factors.**

Descriptors: **Renal insufficiency, acute. Cardiac surgical procedures. Postoperative complications.**

INTRODUCTION

Acute renal failure (ARF) is a syndrome characterized by a rapid reduction in the renal function (hours or weeks) with consequent serum retention of nitrated products such as urea and creatinine, with a potentially reversible character after control of the triggering factor. The disease occurs in approximately 5% of patients in tertiary hospitals and in up to 30% of patients in intensive care units (ICUs) [1,2]. In several studies performed by the Nephrology Section of the Medical School in Botucatu (FMB-UNESP), an increase in 30% of the basal value of serum creatinine was considered the standard level to diagnose ARF [3,4]. It is a consensus in publications that ARF is an independent risk factor for death and is also associated to a prolonged hospitalization for survivors [5]. In spite of advances in the management of these patients, mainly in respect to dialytic treatment, mortality remains at around 50% of the cases and can reach 80% in the ICU [6]. Patients with heart disease present with high risk of ARF, in particular due to hemodynamic involvement, the use of endovenous contrast, arterial catheterism with risk of atheroembolism and the frequent use of angiotensin converting enzyme inhibitors.

Several studies evaluated the risk factors for the development of ARF after heart surgery. Chertow et al. [7] found, as the main variables associated with ARF, a reduction in the heart outflow, congestive heart disease, perioperative acute myocardial infarction, the use of cardiopulmonary bypasses (CPB), neurological alterations and mediastinitis. Behrend & Miller [8] studying 2392 patients admitted in Heart Care Units in the USA found an incidence of 17% of ARF with the main etiologies being hemodynamic alterations (54%), the use of contrast (11%), sepsis (6%), post-renal obstructions (3%) and multifactorial conditions (26%). Similar to other studies, death of patients with ARF was much higher when compared to those that did not present with renal dysfunction (50% and 8%, respectively), with the main risk factors for death being oliguria, prolonged mechanical ventilation and the reduction of the heart function.

Data from the literature show that the incidence of ARF is between 0.7% and 31% in patients submitted to heart surgery, 1% to 5% of which evolve with significant renal disease with the necessity of dialysis therapy (dialytic ARF) which increases considerably postoperative death that can reach as high as 60 to 80% [5,6,9,10]. Thus, it seems clear that the presence of ARF is an indicator of the severity and/or complicated course of disease associated with a greater utilization of hospital resources and an increase in death rates.

The aim of this work is to prospectively identify the preoperative risk factors for the development of ARF in patients submitted to heart surgery in the Hospital das Clinicas Medical School in Botucatu – UNESP.

METHOD

This was a prospective study in which patients hospitalized for elective heart surgery on the Cardiac and Thoracic Ward of the Hospital das Clinicas of FMB-UNESP were evaluated. The study took place for 21 months from

March 2001 to November 2003. Exclusion criteria included emergency heart surgery due to trauma, under 12-year-old children, patients with end-stage chronic renal failure in renal substitute treatment (dialysis or renal transplant).

After clinical and laboratorial evaluation, medications that might interfere with the surgical procedure were suspended including antihypertensive agents, oral hypoglycemiants, digitalis, oral anticoagulants and antiplatelet medicines. The study protocol consisted in an evaluation and follow-up instrument of patients 48 hours before the procedure, on starting the procedure and 48 hours after the procedure with all evaluations made by the same nephrologist. All patients signed written consent forms.

The protocol included:

a) Gender, age, weight, date of the first evaluation, main cardiological diagnosis, comorbidities and complementary examinations performed within one month before hospital admittance (serum creatinine, total cholesterol and fractions, triglycerides, fasting glycemia, chest x-ray and echocardiography);

b) Laboratorial evaluations performed within 24 hours before the surgical procedure: serum creatinine. After obtaining the serum creatinine, a calculation of the glomerular filtration was made using the Cockroft-Gault equation [11];

c) Identification of possible risk factors for the development of ARF obtained from information provided by the patient, data from the physical and complementary examinations performed within one month prior to the evaluation (results obtained by consulting the patient's records in the institution):

C.1 Indirect cardiological preoperative factors:

i. Arterial hypertension: arterial pressure = 140 x 90 mmHg for patients not taking antihypertensive medicine or any other pressure for those taking antihypertensive agents (IV Brazilian Guidelines on Arterial Hypertension, 2002);

ii. Dyslipidemia: measurement of low-density lipoproteins (LDL cholesterol) > 130 mg/dL or serum triglycerides > 200 mg/dL without the use of medication or any other value of LDL-cholesterol and serum triglycerides for patients taking medicine to reduce these substances (III Brazilian Guidelines on Dyslipidemia, 2001);

iii. Diabetes mellitus: fasting glycemia > 125 mg/dL in two consecutive measurements or any level of glycemia for patients taking oral hypoglycemiants or insulin (Consensus on Diabetes Mellitus, 2002);

iv. Peripheral vascular disease: clinical diagnosis based on patient's complaint and on the physical examination by measurement of the peripheral pulses or by complementary examinations ("Doppler" of the lower limbs);

v. history of encephalic vascular disease;

vi. Prior chronic renal failure: defined by two biochemical parameters independent of the presence of clinical signs and symptoms of renal disease: serum creatinine > 1.4 mg/dL; and calculation of the estimate of glomerular filtration using the Cockroft-Gault equation [11]. According to this estimation the glomerular filtration was classified as: normal (= 90 mL/min/1.73m^2), slightly altered (60 to 89 mL/min/1.73m^2) and moderately altered (30 to 59 mL/min/1.73m^2);

C.2 Preoperative cardiological factors:

i. Presence of angina pectoris: prior history of typical thoracic pain;

ii. Previous acute myocardial infarction;

iii. Cardiomegaly: detected by radiography or echocardiography;

iv. Previous heart surgery;

v. Ejection fraction < 55% at echocardiography;

vi. Class of congestive heart failure (New York Heart Association – NYHA) and the type of surgery to be performed (CABG, valve implantation, valvuloplasty or others).

C.3 Laboratorial evaluation of serum creatinine performed at 24 and 48 hours after the surgery.

The protocol of the study was completed 48 hours after the surgical procedure, followed the conditions set down by the National Health Counsel and was approved by the Research Ethics Committee of the Medical School in Botucatu (UNESP). The nature of the research was duly explained to participating patients who signed written consent forms.

Statistical analysis

Analysis of the data was made using the STATA computer program version 8.0 (STATACORP, 2004) and the data were reported as means ± standard deviation or medians.

Measurements of central tendency and spread were calculated for the numeric variables and frequencies for categorical variables, with a descriptive analysis of the sample. The occurrence of ARF was established as the dependent variable.

The ages of the patients in relation to the presence or absence of ARF were compared using the Student T-test. Preoperative, 24-hour and 48-hour serum creatinine levels in relation to the presence or absence of ARF were compared utilizing the Mann-Whitney test. The comparison of the preoperative, 24-hour and 48-hour serum creatinine levels among patients who evolve with ARF was achieved by the Kruskal-Wallis test with multiple comparisons by the Dunnett method, which was also performed for patients who evolved with preserved renal function. The statistical significance of association between independent variables and the occurrence of ARF was assessed using the chi-squared test with a statistical difference for p-value = 0.05 being considered significant [12]. Relative risks (RR) and Odds ratios (OR) were calculated for each variable that

proved to be significant in the chi-squared test. Multivariate analysis was made by the construction of a logistic regression model with calculations of the adjusted OR. All the independent variables that proved to be associated with the outcome with a p-value = 0.25 were included in the model [13]. Variables which continued with a result after adjustment with p-value = 0.05 remained in the final model.

RESULTS

In this period, 150 patients were accompanied with characteristics as shown in Table 1.

ARF was diagnosed in 51 (34%) of the patients and the distribution was according to the factors shown in Table 2.

It is interesting to note that the median of the preoperative serum creatinine of the patients who evolved without ARF was statistically lower than the median of the serum creatinine of patients who evolved with ARF (1.1 mg/dL and 1.2 mg/dL, respectively; p-value = 0.004).

Among the indirect cardiological preoperative risk factors for ARF, as shown in Table 3, only peripheral vascular disease was associated with a higher occurrence of ARF presenting a RR of 2.5 and a p-value = 0.05. The other risk factors did not present with any association with a higher occurrence of ARF. These included arterial hypertension, dyslipidemia, diabetes mellitus, history of strokes, chronic renal failure, chronic obstructive pulmonary disease and smoking.

In the final logistic regression model (Table 4) for the factors related to the development of ARF, being male presented with a RR of 1.4 and a p-value = 0.04. However, due to the large confidence interval, we can not consider this to be a significant risk factor for the development of perioperative ARF.

Table 1. Characteristics of the study sample and comorbidities

Characteristics	N	%
Gender		
Male	85	57
Age (years)	56 ±15	
Main diagnosis		
Coronary artery insufficiency	99	66
Valve disease	51	34
Median serum creatinine (mg/dL)	1.1	
Co-morbidities	N	%
Arterial hypertension	90	60
Smoking	77	52
Congestive heart failure	73	49
Dyslipidemia	55	37
Previous acute myocardial infarction	48	32
Diabetes mellitus	31	21
Peripheral vascular disease	9	6
Chronic renal failure:		
• Elevation of the serum creatinine	9	6
• Slight alteration in estimated glomerular filtration	53	35
• moderate alteration in estimated glomerular filtration	37	24
Previous stroke	8	6
Chronic obstructive pulmonary disease	3	2

Table 2. Characteristics of the study sample according to the absence and presence of acute renal failure

	ARF			
Characteristics	Absence n=99	Presence n=51	Total patients	p
	(%)	(%)		
Gender				
• Male	52 (61)	33 (39)	65	0.13
• Female	47 (72)	18 (28)	85	_
Diagnosis				
• Coronary artery insufficiency	63 (64)	36 (36)	99	0.43
• Valve disease	36 (70)	15 (30)	51	_
Age (years)	58 ± 14	55 ± 14	_	0.59
Age group				
• ≤ 60 years	60 (71)	24 (29)	84	0.09
• > 60 years	39 (59)	27 (41)	66	_
Preoperative creatinine (mg/dL) *	1.1	1.25	_	0.004
Serum creatinine 24 hours after surgery (mg/dL) *	1.1	1.75	_	< 0.001
Serum creatinine 48 hours after surgery (mg/dL)	0.9	1.85	_	< 0.001

** Values expressed as medians*

Table 3. Association of possible cardiological and indirect cardiological risk factors with the development of acute renal failure in the study sample

INDIRECT CARDIOLOGICAL FACTORS		ARF n(%)	Total	p
Arterial hypertension	YES	30 (33)	90	0.77
	NO	21 (36)	60	_
Dyslipidemia	YES	21 (38)	55	0.43
	NO	30 (32)	95	_
Diabetes mellitus	YES	11 (35)	31	0.86
	NO	40 (34)	119	_
Peripheral vascular disease	YES	7 (78)	9	0.005
	NO	45 (31)	141	_
Previous stroke	YES	4 (50)	8	0.33
	NO	47 (33)	142	_
Chronic renal failure *	YES	2 (22)	9	0.43
	NO	49 (35)	141	_
Chronic obstructive pulmonary disease	YES	1 (33)	3	0.97
	NO	50 (34)	147	_
Smoking	YES	28 (36)	77	0.57
	NO	23 (32)	73	_
CARDIOLOGICAL FACTORS		ARF n(%)	Total	p
Angina "pectoris"	YES	30 (36)	83	0.58
	NO	21 (32)	67	_
Cardiomegaly	YES	25 (41)	62	0.14
	NO	26 (30)	88	_
Prior acute myocardial infarction	YES	20 (42)	48	0.16
	NO	30 (30)	101	_
Previous heart surgery	YES	5 (38)	14	0.73
	NO	46 (34)	136	_
Ejection fraction < 55%*	YES	12 (55)	22	0.07
	NO	38 (35)	111	_

* Defined as preoperative serum creatinine above 1.4 mg/dL

Table 4. Relative risk (RR), Odds ratio (OR) and adjusted OR by logistic regression for the development of acute renal failure:

Variable	RR (CI)	OR bruta (CI)	OR adjusted	p
Peripheral vascular disease	2,5 (1,6-3,8)	7,6 (1,4-40,3)	10,8 (1,7-69,0)	0,01
men	1,4 (0,8-2,2)	1,7 (0,8-2,2)	2,4 (1,0-5,4)	0,04

DISCUSSION

This prospective cohort short study was performed with the objective of identifying preoperative risk factors for the development of ARF in patients submitted to heart surgery. After multivariate analysis, only the presence of peripheral vascular disease was an identified preoperative factor.

There are many published articles that studied the relationship between heart surgery and the occurrence of ARF. The first works, performed about 30 years ago, were retrospective evaluating both dialytic ARF and less severe renal failure without the necessity of dialysis (non-dialytic ARF) [14-16]. In 1998, Chertow et al. [7] published a large prospective multicenter study, in which, apart from evaluating risk factors for dialytic ARF, an algorithm for risk stratification was also presented. Later, other works validated this algorithm in different populations [10,17].

The mechanisms that lead to ARF after heart surgery are little understood, but it is believed that renal ischemic injury resulting from inadequate perfusion, is the main factor, with the action of exotoxins (antibiotics, anesthetic agents, contrast and diuretics) and endotoxins (myoglobin among others) being contributing factors. Chertow et al. [7] proposed that ARF after heart surgery is associated to two main factors: hidden renal ischemia (secondary to reduced heart function, atherosclerotic disease of the renal artery and prolonged ischemia) and reduced renal reserve.

One central consideration in the analysis of ARF after heart surgery is its definition. Several authors utilize the term "renal dysfunction" for non-dialytic ARF, defining it as the presence of serum creatinine increases of around 25 to 50% of the preoperative value and the term "renal failure" for patients with dialytic ARF [5-9,18,19]. Although it seems more objective, the definition of ARF based on dialysis also depends on the experience of the nephrology team, although defined classical criteria are followed. Thus, the incidence and risk factors of this disease after heart surgery show much variability. In this work, ARF was defined as a 30% increase in the basal value on the first or second postoperative day, which occurred in 34% of the patients; an incidence higher than in published works that report variations between 1% and 30% [5-9,18,20].

The period of evaluation of the renal function is based on a study by Stafford [21], whose analysis of serum creatinine of patients who later developed ARF obeyed the elevations of serum creatinine on average 48 hours after the heart surgery procedure, and returned to basal values after 45 days in cases that evolved without the necessity of dialysis.

Although performed with a small number of patients, this work shows results similar to several other studies, including many multicenter studies. Abel et al. [22] evaluated 500 patients submitted to heart surgery with 20% presenting with slight azotemia, 7% with moderate or severe ARF (defined as serum creatinine > 5 mg/dL) and 3% dialytic ARF. Risk factors reported in this study were advanced age, previous renal dysfunction, surgery time, and use of CPB, intra-aortic balloon and aortic clamping. Conlon et al. [5] studied the incidence and main risk factors for the development of ARF (defined as an increase equal to or greater than 1 mg/dL of the basal serum level), of 2844 patients submitted to heart surgery in the US over two years. In this study, increased ages, previous renal dysfunction, CPB time, the presence of carotid murmur and of diabetes mellitus and a reduction if the ejection fraction were independent factors associated with ARF, whose incidence was 8% for non-dialytic ARF and 0.7% for dialytic ARF. Mangano et al. [9] studied 2222 patients submitted to heart surgery with an incidence of dialytic ARF of 1.4% and non-dialytic (increase of at least 62 µmol/L in serum creatinine) of 7.7%. After multivariate analysis, the main factors involved with the development of ARF were congestive heart failure, age equal to or greater than 80 years old, the use of intra-aortic balloon, moderate ventricular dysfunction, preoperative elevation of the serum creatinine, CPB time, presence of fasting glycemia greater than 16 mmol/L, prior CABG and a history of type I diabetes mellitus. Chertow et al. [7], in a prospective cohort multicenter study of 42773 patients, identified an incidence of dialytic ARF of 1.1% with the main risk factors being valve surgery (when compared with CABG), previous renal failure (evaluated by estimated glomerular filtration), the use of intra-aortic balloon, history of heart surgery, Functional Class IV heart failure, peripheral vascular disease, ejection fraction < 35%, chronic obstructive pulmonary disease and systolic arterial hypertension.

Age is a frequently studied risk factor without consensus. While Chertow et al. [7] demonstrated an evident relationship between the increase in age and the incidence of dialytic ARF, Van den Noortgate et al. [19] did not find any significant difference in patients with ages equal to or greater than 70 years old, when compared to under 70-year-olds, in a retrospective study of 3736 adults. The current work did not show any relationship between ARF and age. Patients with ages equal to or greater than 60 years old did not present with a higher incidence of ARF when compared with younger patients, probably as the sample of patients was relatively young with a mean age of about 56 years old.

Some works, have identified being female as a risk factor for ARF after heart surgery, although in this work being male, after the multivariate analysis presented with a tendency to develop ARF, although this was not statistically confirmed. Thakar et al. [23], analyzing 24601 patients submitted to heart surgery, showed that being female was an independent risk factor for developing both dialytic and non-dialytic ARF (defined as a drop of at least 50% of

estimated glomerular filtration), with a RR of 1.6 in relation to men. Other authors [7,10] did not identify significant differences in the incidence of ARF between men and women. In general, epidemiological studies associate a higher incidence of ARF to men [24]. Further studies should be performed to confirm the influence of gender on the development of ARF after heart surgery.

In respect to preoperative renal function, several authors have shown that previous chronic renal dysfunction is an important risk factor to aggravate the postoperative evolution after heart surgery [7,23], which also occurred in the current study where the median increase in the preoperative serum creatinine was associated to a greater development of ARF, suggesting that the increased value of creatinine, obtained immediately before surgery may be indicative of the occurrence of ARF. However, there was no significant association between the occurrence of ARF and prior drop in the glomerular filtration as estimated by the Cockcroft-Gault equation [11]. Although it is not the gold standard to measure renal function, as patients with an increase in weight secondary to edema, may have an unreal increase in the estimated glomerular filtration, this formula has been used in several works and may complement the evaluation of renal function. Chertow et al. [7] demonstrated the direct relationship between the pre-surgical drop in estimated glomerular filtration and dialytic ARF in patients submitted to heart surgery. These data may confirm the previously raised hypothesis that the occurrence of ARF after heart surgery is associated with a reduction in the functional renal reserve.

In the current study, peripheral vascular disease was a preoperative risk factor strongly associated with the development of ARF, which was also recently reported by Stallwood et al. [25] as well as other authors. This also occurred in relation to previous CABG and angina indicating that the "atherosclerotic condition" of these patients may predispose them to an acute worsening of the renal function after surgery.

Valve surgery, according to several works, is associated to a higher development of ARF when compared to CABG, but this was not evidenced in the current work. Tuttle et al. [18] showed that patients submitted to valve surgeries presented a 2.5 times higher risk of developing ARF compared to patients submitted to other types of surgery. According to these authors, perhaps the greatest occurrence of ARF is associated with the presence of microthrombi released by the renal tissue during this type of operation. The small sample size in the present study did not allow better evaluation of this risk factor.

It is well known that the evolution of ARF in patients submitted to heart surgery is strongly associated with death [5,7,9,22,23]. Conlon et al. [5] showed that patients submitted to CABG who develop ARF have a 20-fold higher risk of death compared to those who evolve with normal renal function. In the current work, as it is a short prospective cohort (only two days in the postoperative period), it was not possible to analyze mortality in the study population.

The results obtained in the present study enable an identification of some preoperative risk factors involved in the development of ARF after heart surgery. In spite of the sample size not allowing statistical confirmation of other preoperative factors, this study showed a certain tendency of some factors that contribute to the development of ARF in heart surgery. Identifying this at-risk population will enable simple, but important, conducts to prevent acute renal failure in these situations, such as the more careful use of potentially nephrotoxic drugs and performing less aggressive procedures which may contribute to a more satisfactory evolution of the patient in the postoperative period even reducing the mortality rates.

This prospective short cohort study was performed with the objective of identifying preoperative risk factors for the development of ARF in patients submitted to heart surgery. After multivariate analysis, the presence of peripheral vascular disease was an identified preoperative risk factor. Due to the heterogeneity of the patients (a large number of associated diseases) it is possible that the sample size may have impeded the identification of other risk factors.

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