U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO
FISIOPATOLOGIA CARDIOVASCULAR

Acute kidney injury after Coronary Artery Bypass Grafting Surgery: predictors and survival impact

Raquel Soares Moreira

2019

ORIENTADOR:
PROFESSOR DOUTOR ADELINO LEITE-MOREIRA
PROFESSOR CATEDRÁTICO DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO
CO-ORIENTADOR:
PROFESSOR DOUTOR ANDRÉ LOURENÇO
PROFESSOR AUXILIAR DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

AGRADECIMENTOS

Ao Professor Adelino Leite-Moreira, por me conceder a oportunidade de integrar a sua equipa no Departamento de Cirurgia e Fisiologia da Faculdade de Medicina da Universidade do Porto, pela contribuição científica, conhecimento e disponibilidade ao longo de todo este percurso.

Ao Professor André Lourenço, pela coorientação e contributo científicos.

A todos os meus colegas do Departamento de Cirurgia e Fisiologia pelo seu constante apoio e a toda a equipa do Serviço de Cirurgia Cardiotorácica do Centro Hospitalar e Universitário de São João pelo seu apoio logístico.

Aos docentes do Mestrado em Fisiopatologia Cardiovascular, por transmitirem o seu conhecimento e experiência ao longo destes 2 anos.

Aos meus colegas de mestrado, pelo seu companheirismo e amizade desde o primeiro dia.

A todas as minhas colegas de investigação clínica, Soraia Moreira, Ana Filipa Ferreira e Renata Melo, pelo seu constante apoio e alegria, celebrando todos os nossos sucessos.

À Francisca Saraiva, acima de tudo, por acreditar em mim, mas também pela partilha dos seus conhecimentos, disponibilidade e apoio metodológico constantes.

Por fim, à minha família, por estarem presentes em todos os momentos, especialmente à minha mãe que me acompanha em todos os meus percursos, nos momentos mais desafiantes, mas também nos mais felizes, sendo a pessoa que mais me apoia ao longo da minha vida.

ABSTRACT

Introduction: Cardiac surgery may induce acute kidney injury (AKI) and need for renal replacement therapy, being the second most common cause of AKI in the intensive care unit.

Purpose: To determine AKI incidence after coronary artery bypass grafting (CABG) surgery, its predictors and its impact in immediate and long-term survival.

Methods: Retrospective single-center cohort study including all CABG surgeries performed in 2012 and 2013 at Centro Hospitalar e Universitário São João, EPE. Patients on haemodialysis before surgery and off- to on-pump conversions were excluded. AKI was defined as an increase of at least 0.3 mg/dL in creatinine within 48 hours, or an increase to 1.5 times or more from baseline, within 7 days after CABG. Chi-square tests and independent t-tests were used to compare categorical and continuous data, respectively, between patients with and without AKI. A multivariate logistic regression model was used to identify independent risk factors of AKI. To determine the effect of AKI in long-term survival, Kaplan-Meier curves, Log Rank test and multivariate Cox regression (maximum follow-up time: 6 years) were used.

Results: We included 804 patients, mean age 64±10 years, 82% being male. AKI occurred in 89 patients (11%). These patients were older (67±10 vs. 64±10 years, p=0.003), presented more frequently diabetes (51% vs. 39%, p=0.028), recent acute myocardial infarction (AMI; 52% vs. 39%, p=0.025), NYHA functional class III-IV (13% vs. 6%, p=0.034), moderate to severe left ventricular dysfunction (28% vs. 18%, p=0.023), lower haemoglobin and haematocrit (13 g/dL vs. 14 g/dL, p=0.005 and 38% vs. 40%, p=0.005, respectively) and had worse renal function pre-operatively, characterised by a lower glomerular filtration rate (GFR) (82 vs. 91 ml/min/1.73m^2, p<0.001) compared with patients without AKI. In multivariate analysis, age (OR: 1.03, 95% CI: 1.00-1.06, p=0.014), male gender (OR: 2.03, 95% CI: 1.02-4.04, p=0.045), the occurrence of recent AMI (OR: 1.61, 95% CI: 1.01-2.58, p=0.046) and pre-operative serum creatinine (OR: 2.43, 95% CI:1.40-4.23, p=0.002) emerged as independent predictors of AKI. Regarding long-term survival, patients with AKI did not show differences in cumulative survival compared to patients without AKI (86% vs. 90%, Log-rank test p=0.094). AKI was not an independent

predictor of mortality in multivariate Cox regression (HR: 1.31, 95% CI: 0.70-2.48, p=0.400), but was associated with higher early mortality (4.5% *vs*. 0.6%, p=0.007).

Conclusion: At our center AKI incidence after CABG surgery was 11%. Older age, male gender, recent AMI and higher pre-operative serum creatinine were settled as AKI independent predictors. This immediate post-CABG outcome did not show association with mid-term survival, but was related to worse early mortality.

Keywords: acute kidney injury; coronary artery bypass grafting; creatinine; post-operative period.

RESUMO

Introdução: A cirurgia cardíaca pode causar insuficiência renal aguda (IRA) e a necessidade de terapia de substituição renal, sendo a segunda causa mais comum de IRA na unidade de cuidados intensivos.

Objetivo: Determinar a incidência de IRA após cirurgia de revascularização do miocárdio (CRM), os seus preditores e respetivo impacto na sobrevida a médio e longo-prazo.

Métodos: Estudo retrospetivo unicêntrico, incluindo todas as CRM realizadas entre 2012 e 2013 no Centro Hospitalar e Universitário São João, EPE. Foram excluídos os pacientes que se encontravam em hemodiálise pré-operatória e as conversões *off-* para *on-pump*. A IRA foi definida como um aumento na creatinina superior ou igual a 0,3 mg/dL nas primeiras 48 horas após a cirurgia, ou um aumento superior ou igual a 1,5 vezes do valor pré-operatório, dentro de 7 dias após CRM. Foram utilizados testes qui-quadrado e testes t para amostras independentes para comparar variáveis categóricas e contínuas, respetivamente, em pacientes com e sem IRA. Para a identificação dos fatores preditores de IRA foi utilizado um modelo de regressão logística multivariada. Para determinar o efeito da IRA na sobrevida a longo prazo foram utilizadas curvas *Kaplan-Meier*, teste *Log Rank* e regressão multivariada de Cox, (follow-up máximo: 6 anos).

Resultados: Foram incluídos 804 pacientes, com uma média de idade de 64±10 anos, sendo 82% homens. A IRA ocorreu em 89 pacientes (11%). Estes pacientes eram mais velhos (67±10 vs. 64±10 anos, p=0,003), mais frequentemente diabéticos (51% vs. 39%, p=0,028), apresentavam uma maior incidência de enfarte agudo do miocárdio (EAM) nos 90 dias prévios à cirurgia (52% vs. 39%, p=0,025), classe funcional NYHA III-IV (13% vs. 6%, p=0,034), disfunção ventricular esquerda moderada a severa (28% vs. 18%, p=0,023), valores de hemoglobina e hematócrito inferiores (13 g/dL vs. 14 g/dL, p=0,005 e 38% vs. 40%, p=0,005, respetivamente) e pior função renal pré-operatória, caracterizada por uma taxa de filtração glomerular (TFG) inferior (82 vs. 91 ml/min/1.73m^2, p<0,001) quando comparados com os indivíduos sem IRA. Na análise multivariada, a idade (OR: 1,03, 95% IC: 1,00-1,06, p=0,014), género masculino (OR: 2,03, 95% IC: 1,02-4,04, p=0,045), a ocorrência de EAM recente (OR: 1,61, 95% IC: 1,01-2,58, p=0,046) e a creatinina pré-operatória (OR: 2,43, 95% IC:1,40-4,23, p=0,002) emergiram como preditores

independentes de IRA. Relativamente à sobrevida a longo-prazo, os pacientes com IRA não apresentaram diferenças na sobrevida cumulativa comparativamente com os pacientes sem IRA (86% vs. 90%, teste *Log-rank* p=0,094). A IRA não se revelou um preditor independente de mortalidade na regressão multivariada de Cox (HR: 1,31, 95% IC: 0,70-2,48, p=0,400) mas associou-se a uma mortalidade hospitalar mais elevada (4,5% *vs*. 0,6%, p=0,007).

Conclusão: No nosso centro, a incidência de IRA após CRM foi de 11%. A idade avançada, género masculino, EAM recente e creatinina sérica pré-operatória mais elevada foram preditores independentes de IRA. Este *outcome* imediato após CRM não demonstrou estar associado com a sobrevida a médio-prazo, mas associou-se a piores resultados imediatos.

Palavras-chave: insuficiência renal aguda; cirurgia de revascularização do miocárdio; creatinina; período pós-operatório.

INDEX

ACRONYMS

AKI – Acute kidney injury / Group that developed AKI

AKIN – Acute Kidney Injury Network

AMI – Acute Myocardial infarction

AUC – Area under the curve

CABG – Coronary artery bypass grafting

CI - Confidence interval

CKD – Chronic kidney disease

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration equation

CPB – Cardiopulmonary bypass

GFR – Glomerular Filtration Rate

HR – Hazard ratio

IABP – Intra-aortic balloon pump

IBM® SPSS® Statistics - Statistical Package for the Social Sciences

KDIGO – Clinical Practice Guideline for Acute Kidney Injury classification

KDIGO 2012 - Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

nAKI – Group that did not develop AKI

NYHA – New York Heart Association

OR – Odds ratio

RNU - *Registo Nacional de Utentes*

ROC – Receiver operating characteristics

RRT – Renal replacement therapy

RSE - *Registo de Saúde Eletrónico*

SWI – Sternal Wound Infection

FIGURES INDEX

TABLES INDEX

1. INTRODUCTION

Acute kidney injury (AKI) is a frequent complication after cardiac surgery, occurring in up to 40% of patients, and between 6% and 34% after coronary artery bypass grafting (CABG) (1-11). This outcome is related to death rates of 2-4% and a high incidence of other postoperative complications such as stroke or need of renal replacement therapy (RRT) (8, 9). The abrupt worsening of renal function is expressed by a decrease in glomerular filtration rate (GFR), (12) due to renal hypoperfusion and consequently, ischemia-reperfusion cycles, increase in oxidative stress and inflammatory response (2).

In CABG surgery, the association between on- *vs* off-pump technique and AKI is still conflicting. According to some authors, off-pump technique prevents AKI as well as bleeding, need for blood products transfusion (3, 10, 13-16) and need for RRT (17). Other studies showed no difference in AKI incidence, stating that both are equally safe and effective in this setting (17-20).

In addition to surgical technique, other factors had been associated with AKI incidence, namely the presence and severity of pre-operative renal disease, advanced age, female gender, cardiovascular risk factors (hypertension, diabetes *mellitus*), peripheral vascular disease, low pre-operative haemoglobin and haematocrit, left ventricular dysfunction or congestive heart failure, aortic cross-clamping time, emergent surgery and exposure to inotropes or diuretics postoperatively, blood and blood products transfusion (2, 4, 5, 12, 18, 21, 22).

Identification of high risk patients and the use of adequate markers play a key role in this setting (2, 12). Apart from risk factors, renal function deterioration may be undetected in the first 24-48 hours after surgery. Thus, its serial evaluation along hospital stay may be crucial to understand the evolution after cardiac surgery, avoiding the delayed treatment strategy implementation, and consequent acute tubular necrosis.

The main purpose of this study consisted in determining AKI incidence and which are the main pre and peri-operative risk factors related to renal function worsening. We also aimed to

compare survival rates and the incidence of postoperative complications among patients with and without significant renal function worsening in the postoperative period.

2. METHODS

Study design and sample

This is a retrospective single-center cohort study including consecutive patients submitted to isolated first CABG between 2012 and 2013. Emergent off to on-pump conversion, patients in haemodialysis prior to surgery or with missing data on pre-operative renal function status were excluded.

Data collection

To run this study several databases from the Cardiothoracic Surgery department were consulted, namely S*Clínico, Registo de Saúde Eletrónico (RSE), Xcelera*, and *Registo Nacional de Utentes (RNU)*, and a specific database retrospectively filled through the access of patients' clinical files. All-cause mortality was verified in 2017.

Variables

For sample characterisation, the following variables were analysed: demographic and anthropometric data, cardiovascular risk factors, clinical history, current clinical status and urgency of surgery through functional and angina classes, coronary disease severity, results from other medical exams and analytical markers. Peri-operative data consisted in off or on-pump surgical strategy, cardiopulmonary bypass (CPB) and aortic clamping times and number of grafts. To characterise pre-operative and postoperative renal function, serial evaluations were recorded since the pre-operative period and until 6 days after surgery, namely, serum creatinine, GFR (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (23)) and creatinine clearance (Cockcroft-Gault formula (24)). Chronic kidney disease was defined as a GFR of 60 ml/min/1.73m^2 or less pre-operatively, according to KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease classification (KDIGO 2012) (25). AKI diagnosis was made according to the following criteria: increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or ≥ 50% (1.5 times baseline) within 7 days after CABG (Clinical Practice Guideline for Acute Kidney Injury (KDIGO) and Acute Kidney Injury Network (AKIN) criteria (26, 27)). For this, the difference between maximal postoperative and pre-operative

creatinine was calculated in relation to its pre-operative value (Δcreatinine = ((max creat pos – creat pre) / creat pre). This variation also allowed sample stratification in two groups: the group that developed AKI (AKIg) and the group that did not develop (nAKI).

Post-operative complications evaluated included prolonged mechanical ventilation time (> 24h), low cardiac output syndrome requiring intra-aortic balloon pump (IABP) or at least two inotropic agents, re-exploration of thorax due to bleeding or sternal wound infection (SWI), length of in-hospital stay and early mortality (defined as in-hospital death or within 30 days after surgery).

Statistical analysis

Data analysis was performed with IBM® SPSS® *Statistics* (*Statistical Package for the Social Sciences*) Version 24 software.

For sample characterisation descriptive statistics methods were used, namely: absolute frequencies and proportions for categorical variables, as well as central tendency and dispersion measures for continuous variables.

To study associations between independent and dependent variables (AKI) inferential statistics methods were used. Univariate analysis was run using independent samples t tests or Mann-Whitney test, for continuous variables with normal or non-normal distribution, respectively. To compare categorical variables' proportions within groups, chi-square test or Fisher's exact test, if more than 20% of the cells had an expected value of less than 5, were used. Wilcoxon test was performed to compare pre-operative and at discharge creatinine values.

For multivariate analysis logistic regression was used to determine AKI predictors. In these models, CPB, gender, age and other clinically relevant or statistically significant variables in the univariate analysis were considered as independent variables. Logistic models were evaluated concerning associations between covariates and dependent variable (omnibus test, G^2, considered significant if $p<0.05$) and calibration (Hosmer-Lemeshow test) and models' discriminative capacity (area under the receiver operating characteristic curve; (AUC ROC)). Linear regression assumptions were confirmed (normal distribution and constant variance of residues). Beta coefficients (β), odds ratio (OR) and respective 95% confidence intervals (95%CI) were obtained.

To study if AKI had any impact in patients' cumulative survival, univariate analysis followed the same procedures described above, and Kaplan-Meier curves were obtained. To determine if AKI was an independent predictor of mortality, Cox regression was performed and hazard ratios (HR) and respective 95% confidence intervals were obtained.

A significance level of 5% was considered.

Ethics

This study was approved by the Ethics Committee and Administration Council of Centro Hospitalar e Universitário de São João, (Appendixes).

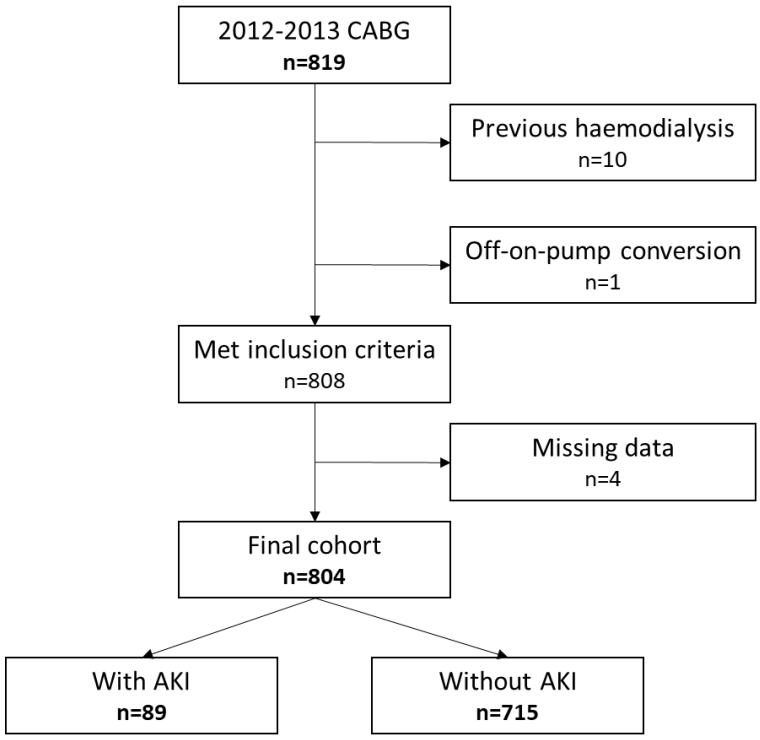
Confidentiality and anonymity of the patients' identifiers were guaranteed, regarding Helsinki's Declaration, (reviewed in Fortaleza in 2013).

Patient informed consent was waived according to observational and retrospective nature of study, based on data routinely registered in the clinical records of each patient that underwent cardiac surgery.

3. RESULTS

Study sample

From the 819 patients enrolled, 10 were excluded because they were on renal replacement therapy, specifically haemodialysis, prior to surgery and 1 that corresponded to an off-on-pump conversion in the operating room, also meeting exclusion criteria. From the 808 patients left, 4 had no recent information relative to their renal function and were also excluded (Figure 1).



AKI – acute kidney injury, CABG – coronary artery bypass grafting.

Figure 1: Study flowchart.

AKI incidence and predictors

Sample baseline characteristics are given in Table 1.

Table 1: Sample characterization and univariate analysis.

Variable	Total n=808	AKI n=89	nAKI n=715	*P*-value
Demographic and body features				
Age (years), mean ± SD	64.4 ± 10.1	67.4 ± 9.9	64.0 ± 10.1	0.003
Male gender, n (%)	658 (81.8)	78 (87.6)	580 (81.1)	0.132
BMI (kg/m^2), mean ± SD	27.5 (3.9)	28.3 (3.6)	27.4 (3.9)	0.064
Obesity (BMI>30 kg/m^2), n (%)	192 (23.9)	26 (29.2)	166 (23.2)	0.214
Comorbidities/preoperative status				
Systemic hypertension, n (%)	621 (77.2)	76 (85.4)	545 (76.2)	0.052
Diabetes Mellitus, n (%)	320 (39.8)	45 (50.6)	275 (38.5)	0.028
Dyslipidemia, n (%)	614 (76.4)	62 (69.7)	552 (77.2)	0.114
Smoking, n (%)	377 (46.9)	39 (43.8)	338 (47.3)	0.538
Cerebrovascular disease, n (%)	76 (9.5)	11 (12.4)	65 (9.1)	0.320
PAD, n (%)	140 (17.4)	17 (19.1)	123 (17.2)	0.656
Recent AMI, n (%)	327 (40.7)	46 (51.7)	281 (39.3)	0.025
CCS IV, n (%)	544 (67.7)	63 (70.8)	481 (67.7)	0.562
NYHA class III or IV, n (%)	56 (7.0)	11 (12.5)	45 (6.4)	0.034
Moderate to severe LV dysfunction, n (%)	147 (18.3)	24 (27.6)	123 (17.5)	0.023
Triple vessel disease, n (%)	597 (74.3)	66 (74.2)	531 (74.3)	0.982
EuroSCORE II, median (min-max)	1.5 (0.5-44.4)	1.7 (0.5-40.2)	1.4 (0.50-44.4)	0.001
CKD (GFR <60 ml/min/1.73m^2), n (%)	339 (42.2)	52 (58.4)	287 (40.1)	0.001
Blood sampling evaluation				
Haemoglobin (g/dL), mean ± SD	13.6 (1.70)	13.0 (1.92)	13.7 (1.66)	0.005
Haematocrit (%), mean ± SD	39.9 (5.1)	38.4 (5.5)	40.1 (5.0)	0.005
Creatinine (mg/dL), median (min-max)	0.8 (0.4-3.6)	1.0 (0.5-3.6)	0.9 (0.4-3.4)	<0.001
GFR (ml/min/1.73m^2), median (min-max)	89.6 (12.2-130.3)	81.5 (16.0-114.0)	90.5 (12.2-130.3)	<0.001
Creatinine clearance (ml/s), mean ± SD	93.3 (33.4)	83.5 (34.0)	94.5 (33.2)	0.004
Surgical features				
Off-pump surgery, n (%)	396 (49.3)	43 (48.3)	353 (49.4)	0.851
CPB time (min), median (min-max)	95 (43-383)	97 (43-177)	94 (51-383)	0.770
Aortic clamping time (min), median (min-max)	60 (29-203)	63 (29-123)	60 (30-203)	0.635
BIMA use, n (%)	377 (46.9)	42 (47.2)	335 (46.9)	0.952

AKI – group that developed acute kidney injury, nAKI – group that did not develop acute kidney injury, AMI – acute myocardial infarction, BIMA – bilateral internal mammary artery, BMI – body mass index, CCS – Canadian Cardiovascular Society, CKD – chronic kidney disease, CPB – cardiopulmonary bypass, GFR – glomerular filtration rate, LV – left ventricular, NYHA, New York Heart Association, PAD – peripheral artery disease, RBC – red blood cells, SD – standard deviation.

Eighty-nine patients (11.1%) developed AKI in the postoperative period. These patients were older, more frequently diabetic and had more frequently acute myocardial infarction 90 days prior to surgery, moderate to severe left ventricular dysfunction and New York Heart Association (NYHA) functional class III or IV. Regarding pre-operative renal function and blood analytic status, AKI group presented more pre-operative chronic kidney disease (CKD) (GFR < 60 ml/min/1.73m^2), lower haemoglobin and haematocrit values. Concerning surgical features there were no significant differences between groups.

In multivariate analysis, older age, male gender, recent myocardial infarction and a higher pre-operative creatinine level emerged as independent risk factors of AKI. The use of CPB was not associated with AKI (Table 2).

Table 2: AKI predictors according to the multivariate logistic regression model (G, p<0.001; HL, p=0.60; AUC: 0.7, 0.6-0.7).

Variable	*P*-value	OR (95% CI)
Age at operation	0.014	1.031 (1.006 - 1.057)
Male gender	0.045	2.026 (1.017 - 4.037)
Diabetes	0.114	1.461 (0.914 – 2.336)
Obesity (BMI ≥ 30kg/m^2)	0.164	1.437 (0.862 – 2.396)
Recent AMI	0.046	1.614 (1.009 – 2.582)
NYHA class III or IV	0.839	1.086 (0.488 – 2.417)
Preoperative creatinine (mg/dL)	0.002	2.434 (1.403 – 4.225)
Off-pump surgery	0.627	0.893 (0.565 – 1.411)

AMI – acute myocardial infarction, BMI – body mass index, CI – confidence interval, NYHA, New York Heart Association, OR – odds ratio.

Postoperative renal function monitoring

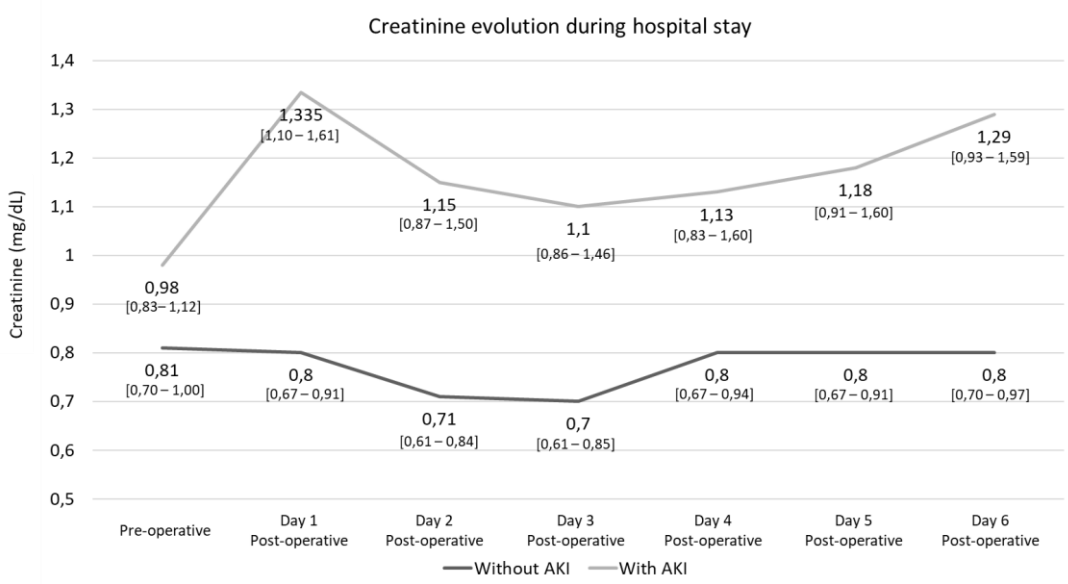
Renal function markers along the postoperative period were monitored in both groups (Table 3 and Figure 2). Two individuals from AKI group required renal replacement therapy. AKI group had a peak creatinine value in the first 24 hours after CABG, while the group that did not develop AKI remained stable until discharge. AKI patients had worse renal function even at discharge, although their renal function had partially recovered until postoperative day 3, they

presented a median of 1.29 mg/dL at discharge, significantly higher than the pre-operative median value 0.98 mg/dL (p=0.009).

Table 3: Postoperative renal function characterisation.

Variable [Median, (min-max)]	Total n=808	AKI n=89	nAKI n=715	*P*-value
Maximum creatinine (mg/dL)	0.9 (0.4 - 5.7)	1.3 (0.8 – 5.7)	0.9 (0.4 – 4.7)	<0.001
Creatinine at discharge (mg/dL)	0.8 (0.3 – 4.6)	1.0 (0.6 – 4.6)	0.8 (0.3 – 3.9)	
GFR at discharge (mg/dL)	90.8 (10.4 – 132.1)	72.5 (11.8 – 114.6)	92.1 (10.4 – 132.1)	
Creatinine clearance at discharge (ml/s)	94.7 (14.5 – 328.5)	75.5 (19.1 – 206.3)	96.8 (14.5 – 328.5)	

AKI – group that developed acute kidney injury, nAKI – group that did not develop acute kidney injury, GFR – glomerular filtration rate



Evolution of median serum creatinine values, (P25-P75), observed during hospital stay for groups AKI and nAKI.

Figure 2: Creatinine follow-up during hospital stay.

Survival analysis

Median follow-up was 4.5 years (4.5 and 4.3 for AKI and nAKI patients, respectively). Overall mortality was 9.1% (n=73) at 6 years of follow-up. Kaplan-Meier curves (Figure 3) demonstrated a worse cumulative survival in AKI group (86%) compared to nAKI (90%) without reaching statistical significance (Log-rank test, p=0.094). After multivariate Cox regression

analysis, AKI was not found to be an independent predictor of mortality (HR: 1.31, 95% CI: 0.70 - 2.48, p=0.400). Pre-operative data including age, smoking habits, NYHA III-IV and severe CKD (HR: 2.074, 95%CI: 1.003 – 4.291, p=0.049) were associated with worse survival (Table 4).

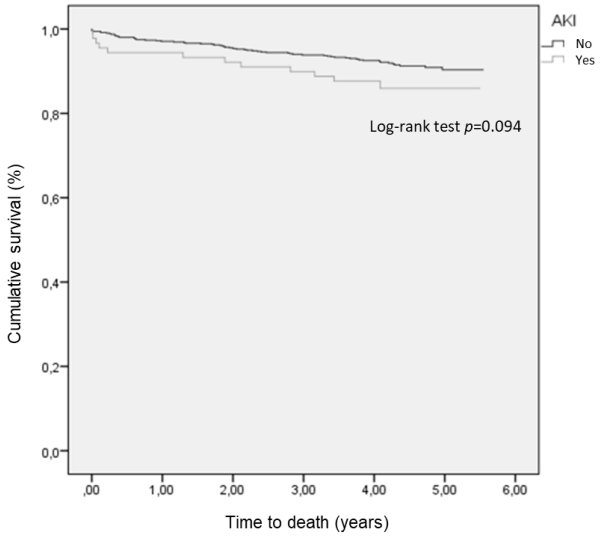


Figure 3: Kaplan-Meier curves comparing cumulative survival between groups.

Table 4: Cox regression model.

Variable	*P*-value	HR (95% CI)
Age at operation	0.004	1.046 (1.014 – 1.079)
Male gender	0.537	0.805 (0.405 – 1.600)
Diabetes	0.469	1.202 (0.731 – 1.974)
Recent AMI	0.357	1.260 (0.771 – 2.060)
Smoking habits or history	0.008	2.108 (1.210 – 3.672)
NYHA class III or IV	0.009	2.388 (1.240 – 4.600)
Creatinine clearance < 50 ml/s	0.049	2.074 (1.003 – 4.291)
Creatinine clearance 50 - 85 ml/s	0.889	0.958 (0.522 – 1.756)
Off-pump surgery	0.431	0.828 (0.518 – 1.325)
AKI	0.400	1.314 (0.696 – 2.479)
Three vessel disease	0.729	1.107 (0.623 – 1.968)

AKI – acute kidney injury, AMI – acute myocardial infarction, CI – confidence interval, NYHA – New York Heart Association, OR – odds ratio.

Postoperative results

The need for inotropic support or IABP after surgery was more frequent in AKI patients. Also, this group of patients had more frequently prolonged ventilation time; longer in-hospital stay and need of thorax re-exploration for bleeding or SWI (Table 5).

Early mortality (during hospital stay or until 30 days) was 1% (n=8), being significantly higher in the AKI group (4.5% *vs*. 0.6%, p=0.007).

Table 5: Postoperative characteristics and univariate analysis.

Variable	Total n=808	AKI n=89	nAKI n=715	*P*-value
Need for IABP, n (%)	17 (2.1)	9 (10.1)	8 (1.1)	<0.001
Inotropic support (≥ 2 amines), n (%)	92 (11.5)	29 (32.6)	63 (8.9)	<0.001
Invasive ventilation time >24 hours, n (%)	25 (3.1)	11 (12.4)	14 (2.0)	<0.001
Time to discharge (days), median (min-max)	7 (3-97)	7 (4-24)	6 (3-97)	0.001
Re-operation on the same episode, n (%)	18 (2.2)	5 (5.6)	13 (1.8)	0.040
Early mortality	8 (1.0)	4 (4.5)	4 (0.6)	0.007

AKI – group that developed acute kidney injury, MAKE – major adverse kidney events, nAKI – group that did not develop acute kidney injury, IABP – intra-aortic balloon pump, RBC – red blood cells.

4. DISCUSSION

Our retrospective observational single center study in patients undergoing CABG found an 11% incidence of AKI, which fits within the range described in the literature, (1, 2, 4, 6, 28). A variety of variables and their association with AKI development and whether this complication after CABG influenced patients' survival and immediate results were studied. Preoperative CKD was determined as an independent predictor of AKI and mid-term survival, while AKI didn't influence mid-term survival but was associated with more post-operative complications, including early mortality.

Concerning AKI predictors, most of our results were in line with the literature. We found a higher probability of AKI according to age of patients, since age is associated with reduced renal reserve, possible atherosclerotic processes in renal arteries (29) and a decrease in the ability of responding adequately to surgical injuries (4, 5, 7, 14, 18, 28, 30). On the contrary, our gender results were not according to the literature. Typically, female gender is associated with a higher incidence of AKI after cardiac surgery supported by a similar mechanism of age, considering the smaller body size of women, (2, 12, 31) but in our cohort, male gender had double risk of AKI emerging as an independent predictor.

Other common AKI risk factors are diabetes mellitus and lower pre-operative haemoglobin and haematocrit. In univariate analysis, AKI patients were more frequently diabetic than patients without AKI, but this risk factor did not have a significant impact in the multivariate analysis. The incipient diabetic nephropathy and microcirculatory changes may be the reason to explain the association between diabetes and postoperative AKI (14, 28) and different diabetes staging across different studies could explain the diverse results in the literature (4).

Regarding pre-operative state, in our sample, the higher the pre-operative serum creatinine level, the higher the probability of AKI. In fact, CKD or, at least, some degree of renal impairment are well established risk factors for AKI, being also predictors of mortality (2, 4, 7, 18, 22, 28, 32), nevertheless an increasing number of patients with some degree of renal dysfunction are being submitted to cardiac surgery (22). CABG cohorts have also a substantial number of patients with recent coronary acute syndromes. About 40% of our sample had an acute myocardial infarct

(AMI) within 90 days prior to surgery and this factor was independently associated with AKI incidence. This finding could be associated with the degree of haemodynamic instability at the time of the procedure, worst disease severity, (28) considering that AKI is also associated with infarct dimension and its microvascular consequences, (33) and the need for contrast agents in the setting of coronary angiography (34), which have nephrotoxic effects (35). The development of heart failure after AMI, requires treatment that includes volume depletion through diuretics use, which are be administered for preload control due to myocardial stunning or even scaring, which favours renal function worsening through its nephrotoxicity (36). This low-flow, or low-cardiac output state contributes to reduced renal flow, compromising GFR (1).

In respect to cardiac surgery, cardiac manipulation, hypotension and reduced cardiac output contribute to a higher inflammatory state that worsen the patient's renal function (19). Specifically, in CABG, on-pump technique is related to a 5-9% incidence of major complications, including need for RRT (17) and off-pump CABG is associated with better outcomes, including less incidence of AKI (13, 16). The maintenance of this discrepancy is lost 1 year after surgery in a post hoc analysis from the CORONARY trial (3). However, this topic remains controversial, since other reports didn't associate off- *versus* on-pump technique with AKI (17-20). Similar to these, our study revealed no impact of this factor on post-operative renal function.

We didn't find, contradicting the literature (7), AKI as an independent predictor of post-discharge mortality, maybe because we didn't consider the time of AKI recovering. In fact, patients with slower AKI reversion may have worse survival because it predisposes them to other organ injuries (37). On the other side, during hospital stay, our AKI patients presented worse outcomes concerning intensive care unit variables, such as prolonged mechanical ventilation time, low-cardiac output syndrome and even higher in-hospital death rates, in line with other reports (4, 32).

Limitations

This study was conducted in a single-center Portuguese tertiary hospital covering only 2 years of CABG surgery with relatively small sample size and limiting the external generalisation

of the results. The retrospective nature of the data leads to some missing in important variables (~1% missing in multivariate analysis performed).

Despite statistical adjustments, residual confounding factors could persist when we tried to estimate AKI predictors and its impact on survival, also due to the unavailability of some important variables such as pre-operative medication and at discharge, results of some blood tests, duration of surgery and blood transfusion.

Different methodological issues across the literature, including AKI definitions and a relatively low percentage of patients with AKI in higher severity stage (n=13/89) contributing to the incidence rates or to different identification of risk factors. Also, it should be reinforced that some patients could present loss of renal function without a direct increase in serum creatinine levels, for instance elderly patients whose muscular mass loss may lead to a decline in serum creatinine levels.

Regarding outcomes, cause of death was not available in all patients, so we restricted our observations to death from all-causes; cerebrovascular complications or myocardial infarction after discharge were not systematically available due to follow-up performed in other centers. Additionally, we did not assess renal function after discharge therefore not allowing to determine if AKI evolved to CKD according to the criteria preconized. In this setting, follow-up time was limited and therefore long-term assessment of the effects of renal function on survival were also not available.

Conclusion

In our cohort AKI after CABG surgery occurred in 11% of the patients. Some variables emerged as AKI predictors, namely: older age, male gender, recent AMI and higher pre-operative serum creatinine, even though long-term survival was not significantly influenced by this outcome. Although our findings provide some evidence that may be considered to improve clinical practice, helping to detect CABG patients at higher risk of AKI and fostering more aggressive preventive strategies in this subset of patients, they must be confirmed with additional studies with larger sample sizes before solid conclusions are drawn.

REFERENCES

1. Chew STH, Hwang NC. Acute kidney injury after cardiac surgery: a narrative review of the literature. Journal of cardiothoracic and vascular anesthesia. 2018.
2. O'Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: current understanding and future directions. Critical Care. 2016;20(1):187.
3. Garg AX, Devereaux PJ, Yusuf S, Cuerden MS, Parikh CR, Coca SG, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. Jama. 2014;311(21):2191-8.
4. Santos FO, Silveira MA, Maia RB, Monteiro MDC, Martinelli R. Acute renal failure after coronary artery bypass surgery with extracorporeal circulation: incidence, risk factors, and mortality. Arquivos brasileiros de cardiologia. 2004;83(2):145-9.
5. Perek B, Maison D, Budnick S, Gębala K, Casadei V, Dadej D, et al. Preoperative blood morphology and incidence of acute kidney injury after on-pump coronary artery bypass grafting–a single-center preliminary report. Kardiochirurgia i torakochirurgia polska= Polish journal of cardio-thoracic surgery. 2018;15(1):18.
6. Rydén L, Sartipy U, Evans M, Holzmann MJ. Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. Circulation. 2014;130(23):2005-11.
7. Antunes PE, Prieto D, De Oliveira JFo, Antunes MJ. Renal dysfunction after myocardial revascularization. European journal of cardio-thoracic surgery. 2004;25(4):597-604.
8. Rydén L, Ahnve S, Bell M, Hammar N, Ivert T, Holzmann MJ. Acute kidney injury following coronary artery bypass grafting: early mortality and postoperative complications. Scandinavian Cardiovascular Journal. 2012;46(2):114-20.
9. Nina VJdS, Matias MM, Brito DJdA, Figueiredo Neto JAd, Coutinho LB, Rodrigues RF, et al. Acute kidney injury after coronary artery bypass grafting: assessment using RIFLE and AKIN criteria. Brazilian Journal of Cardiovascular Surgery. 2013;28(2):231-7.
10. Moradian ST, Ebadi A, Faizi F, Motamedi MHK, Ghiasi MS. The Incidence of Acute Kidney Injury after Coronary Artery Bypass Surgery with or without Cardiopulmonary Bypass. Journal of Critical Care Nursing. 2016;9(4).
11. Massoudy P, Wagner S, Thielmann M, Herold U, Kottenberg-Assenmacher E, Marggraf G, et al. Coronary artery bypass surgery and acute kidney injury—impact of the off-pump technique. Nephrology Dialysis Transplantation. 2008;23(9):2853-60.
12. Mao H, Katz N, Ariyanon W, Blanca-Martos L, Adýbelli Z, Giuliani A, et al. Cardiac surgery-associated acute kidney injury. Cardiorenal medicine. 2013;3(3):178-99.

13. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. New England Journal of Medicine. 2012;366(16):1489-97.

14. Abu-Omar Y, Taghavi FJ, Navaratnarajah M, Ali A, Shahir A, Yu LM, et al. The impact of off-pump coronary artery bypass surgery on postoperative renal function. Perfusion. 2012;27(2):127-31.

15. van Dijk D, Nierich AP, Jansen EWL, Nathoe HM, Suyker WJL, Diephuis JC, et al. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. Circulation. 2001;104(15):1761-6.

16. Seabra VF, Alobaidi S, Balk EM, Poon AH, Jaber BL. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. Clinical Journal of the American Society of Nephrology. 2010;5(10):1734-44.

17. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, et al. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. New England Journal of Medicine. 2016;375(24):2359-68.

18. Elmistekawy E, Chan V, Bourke ME, Dupuis J-Y, Rubens FD, Mesana TG, et al. Off-pump coronary artery bypass grafting does not preserve renal function better than on-pump coronary artery bypass grafting: results of a case-matched study. The Journal of thoracic and cardiovascular surgery. 2012;143(1):85-92.

19. Singh RS, Thingnam SKS, Mishra AK, Verma I, Kumar V. Renal function after off-pump versus on-pump coronary artery bypass grafting. Asian Cardiovascular and Thoracic Annals. 2017;25(7-8):504-8.

20. Hussain G, Azam H, Baig MAR, Ahmad N. Early outcomes of on-pump versus off-pump Coronary Artery Bypass Grafting. Pak J Med Sci2016;32(4):917-921.

21. Shin SR, Kim WH, Kim DJ, Shin I-W, Sohn J-T. Prediction and prevention of acute kidney injury after cardiac surgery. BioMed research international. 2016;2016.

22. Cooper WA, O'brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. Circulation. 2006;113(8):1063-70.

23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

24. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine^{o}. Nephron. 1976;16:31-41.

25. Eknoyan G, Lameire N. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Official Journal of the International Society of Nephrology - Kidney International Supplements. 2013;3(1):1 -163.

26. Kellum JA, Lameire N. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Official Journal of the International Society of Nephrology - Kidney International Supplements. 2012;2(1):1-138.

27. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Critical care. 2007;11(2):R31.

28. Olsson D, Sartipy U, Braunschweig F, Holzmann MJ. Acute kidney injury following coronary artery bypass surgery and long-term risk of heart failure. Circulation: Heart Failure. 2013;6(1):83-90.

29. Bove T, Monaco F, Covello RD, Zangrillo A. Acute renal failure and cardiac surgery. HSR Proceedings in Intensive Care & Cardiovascular Anesthesia. 2009;1(3):13-21.

30. Turney JH. Acute renal failure—A dangerous condition. Jama. 1996;275(19):1516-7.

31. Thakar CV, Liangos O, Yared J-P, Nelson D, Piedmonte MR, Hariachar S, et al. ARF after open-heart surgery: Influence of gender and race. American journal of kidney diseases. 2003;41(4):742-51.

32. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute kidney injury after cardiac surgery focus on modifiable risk factors. Circulation. 2009;119(4):495-502.

33. Reinstadler SJ, Kronbichler A, Reindl M, Feistritzer H-J, Innerhofer V, Mayr A, et al. Acute kidney injury is associated with microvascular myocardial damage following myocardial infarction. Kidney international. 2017;92(3):743-50.

34. Khan I, Dar MH, Khan A, Iltaf K, Khan S, Falah SF. Frequency of acute kidney injury and its short-term effects after acute myocardial infarction. Hypertension. 2017;114:55-10.

35. Giacoppo D, Madhavan MV, Baber U, Warren J, Bansilal S, Witzenbichler B, et al. Impact of contrast-induced acute kidney injury after percutaneous coronary intervention on short- and long-term outcomes: pooled analysis from the HORIZONS-AMI and ACUITY trials. Circulation: Cardiovascular Interventions. 2015;8(8):e002475.

36. Sun Y-B, Liu B-C, Zou Y, Pan J-R, Tao Y, Yang M. Risk factors of acute kidney injury after acute myocardial infarction. Renal failure. 2016;38(9):1353-8.

37. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. The Annals of thoracic surgery. 2010;90(4):1142-8.

APPENDIXES

Appendix 1 – Ethics Committee Authorisation

Parecer

Título do Projecto: Estudo retrospectivo dos resultados da cirurgia de revascularização do miocárdio no Centro Hospitalar de S. João

Nome do Investigador Principal: Adelino Leite Moreira

Entidade Promotora: NA

Serviço onde decorrerá o Estudo: Serviço de Cirurgia Cardiotorácica do Centro Hospitalar de São João e Departamento de Fisiologia e Cirurgia Cardiotorácica da Faculdade de Medicina do Porto

Objectivo e concepção do Estudo:

São objectivos deste projecto de investigação identificar e analisar os dados clínicos, sociodemográficos e cirúrgicos e avaliar o seu impacto nos resultados da cirurgia de revascularização do miocárdio.

Trata-se de um estudo de coorte retrospectivo e analítico, prevendo a selecção de indivíduos submetidos no Centro Hospitalar de S. João a cirurgia de revascularização do miocárdio isolada, no período 2004-2013.

Na sua metodologia, inscreve-se o acesso aos processos clínicos dos participantes e a base de dados hospitalares, nomeadamente o SAM, o *xcelera* e o *Cardia*, para recolha de dados clínicos, demográficos, cirúrgicos e de exames complementares de diagnóstico e terapêutica. Estão exaustivamente descritos no Protocolo da Investigação os dados a recolher. Ainda, será aplicado por via telefónica um inquérito aos participantes, para cuja colaboração está prevista a obtenção de consentimento verbal. O inquérito a aplicar está anonimizado e adequa-se aos objectivos da investigação.

- Considerando que serão acedidos os dados clínicos de doentes do CHSJoão, foi solicitada informação sobre o perfil e a relação profissional com a Instituição dos diferentes elementos da equipa de investigação, já que, dos 9 elementos que integram a equipa, apenas 3 são médicos do Serviço. A este pedido, recebemos esclarecimento satisfatório do investigador, nomeadamente os respectivos perfis profissionais e a declaração de confidencialidade como membros da equipa de investigação.
- Na abordagem telefónica que será feita aos participantes, foi devidamente clarificada pelo investigador a forma como será respeitada a confidencialidade.

O projecto de investigação colheu a anuência do Sr. Director de Serviço.

Benefício/risco: Não se referem benefícios nem riscos ao estudo, dada a sua natureza

Respeito pela liberdade e autonomia do sujeito de ensaio: Será solicitado consentimento informado verbal aos participantes para responder por via telefónica ao inquérito previsto para aplicar.

Confidencialidade dos dados: É afirmado que "*todos os dados passíveis de identificação dos participantes (nome, morada) não serão utilizados directamente, mas a partir de codificações*". É assegurada pelo Investigador principal a confidencialidade que toda a equipa dedicará aos dados a que tiver acesso.

Elo de ligação: NA

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Do investigador, estando prevista a publicação dos resultados da investigação

Curriculum do investigador: Adequado à investigação

Data previsível da conclusão do estudo: Dezembro de 2015

Conclusão:

> Dada a natureza e os objectivos do estudo, e considerando os esclarecimentos prestados pelo investigador relativamente às questões enunciadas no parecer preliminar, proponho um parecer favorável à realização deste projecto de investigação, na sua actual definição metodológica.

Porto e H.S.João, 2013-10-25

O Relator

Doutor Filipe Almeida

Appendix 2 – Administration Council Authorisation

CES 279-13

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 09 JAN 2014

Ao CA
c/c Comissão de Ética
3.1.

Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Professor Doutor Adelino Leite Moreira

Título do projecto de investigação: Estudo retrospetivo dos resultados da cirurgia de revascularização do miocárdio no Centro Hospitalar São João E.P.E.

Pretendendo realizar no(s) Serviço(s) de Cirurgia Cardiotorácica do Centro Hospitalar de S. João – EPE e Departamento de Fisiologia e Cirurgia Cardiotorácica da Faculdade de Medicina da Universidade do Porto o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.
Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 27 / Setembro / 2013

O INVESTIGADOR/PROMOTOR

Comissão de Ética para a Saúde do Centro Hospitalar de S. João – EPE
Modelo CES 01

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☒
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Adelaide Vita Soares,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 27 / setembro / 2013

O Investigador Principal

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 2013 / Outubro / 23

Considerando que foram cumpridas as esclarecimentos prestados pelo investigador

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Alves
Presidente da Comissão de Ética

VI