Study Document Cover Page

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Akdeniz University Faculty of Medicine, Department of Anesthesiology and Reanimation

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Study Protocol

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1. Study Objective

This study aims to analyze the effects of cardiovascular autonomic neuropathy (CAN) on primary outcome of acute kidney injury (AKI) and secondary outcome parameters in patients undergoing coronary artery bypass grafting (CABG) with extracorporeal circulation (ECC).

Specifically, the study will investigate:

The incidence of CAN in patients scheduled for isolated CABG

The effect of CAN on AKI

The impact of CAN on outcome parameters (mortality and morbidity)

The relationship between changes in regional cerebral oxygen saturation (rSO_2) and CAN

CAN Diagnosis:

1. Valsalva maneuver
2. Sitting-to-standing test
3. Temperature sensitivity test

2. Materials and Methods

This is a prospective multicenter study including all patients scheduled for CABG requiring ECC. Preoperative CAN diagnosis will be performed 1 day before surgery using Valsalva maneuver, sitting-to-standing test, and temperature sensitivity test. A positive result in at least two tests will confirm CAN.

Preoperative data to be recorded:

Demographics and comorbidities (hypertension, diabetes, COPD, recent MI, atrial fibrillation, dyslipidemia)

Kidney function (BUN, creatinine, GFR)

Hemodynamic parameters before anesthesia induction

Baseline rSO_2 (monitoring will be blinded for clinical purposes)

Intraoperative data:

Hemodynamics, urine output, blood gases

Total cardiopulmonary bypass time, aortic cross-clamp time

Number of coronary artery anastomoses

Postoperative data:

rSO_2 at 1st and 4th hours, and 60 minutes after extubation

Intubation duration, prolonged mechanical ventilation, inotropic agent use

Renal function (BUN, creatinine, GFR) and urine output at 24, 48 hours, and 7th day per KDIGO criteria

Postoperative complications (reoperation, mediastinitis, perioperative MI, neurological complications)

Transfusion volume, IABP use, drainage volume

ICU and hospital length of stay, mortality

3. Acute Kidney Injury (KDIGO Criteria)

Stage	Serum Creatinine	Urine Output
1	1.5–1.9× baseline or >0.3 mg/dL increase	<0.5 mL/kg/hr for 6 hrs
2	2.0–2.9× baseline	<0.5 mL/kg/hr for 2 consecutive 6-hr periods
3	≥3× baseline or >4 mg/dL or RRT initiation	<0.3 mL/kg/hr for ≥24 hrs or anuria ≥12 hrs

4. Intraoperative Management

IV crystalloid infusion ≥100 mL/h from anesthesia induction

Mean arterial pressure maintained between 60–100 mmHg

If MAP <60 mmHg → 5 mg ephedrine

Inotropic agents per standard clinical practice

Transfusion if Hct <27%

Hourly urine output monitoring

ECC pump flow >1.8 L/m²/min

Body temperature during ECC ≥28°C

6. Outcomes

Intubation duration

Prolonged mechanical ventilation

Inotropic agent use

Renal failure (KDIGO criteria)

Neurological injury (stroke, confusion, agitation, memory loss, seizure, neurocognitive dysfunction)

Reoperation

Mediastinitis

Transfusion requirement

IABP use

Postoperative drainage

Perioperative MI

ICU and hospital length of stay

Mortality

7. Inclusion and Exclusion Criteria

Inclusion:

All patients >18 years old scheduled for CABG requiring ECC

Exclusion:

Emergency or revision surgeries

Orthopedic issues preventing standing test

Chronic respiratory diseases (bronchitis, asthma, COPD) affecting Valsalva reliability

Uncontrolled hypertension

Use of antiarrhythmic drugs affecting heart rate-based tests

Chronic kidney failure

Statistical Analysis Categorical variables will be presented as counts and percentages. Between-group comparisons for categorical variables will be performed using the chi-square test. The distribution of continuous variables will be evaluated using skewness and kurtosis. Variables with distribution between -1.5 and +1.5 will be considered normally distributed (parametric), otherwise non-parametric. Parametric continuous variables will be expressed as mean ± SD. Between-group comparisons will be performed using the independent Student's t-test, and within-group temporal comparisons using the paired Student's t-test. Non-parametric continuous variables will be presented as median and interquartile range (IQR). Between-group comparisons for non-parametric variables will be performed using the Mann-Whitney U test, and within-group temporal comparisons using the Wilcoxon signed-rank test. Correlation analysis will be conducted using Pearson (parametric) or Spearman (non-parametric) correlation coefficients. Factors affecting AKI and neurological complications will be evaluated using multiple regression analysis.

Sample Size Calculation The primary objective of this study is to compare the incidence of AKI between CAN-positive and CAN-negative patients undergoing coronary artery bypass grafting (CABG). Based on previous studies using heart rate variability (HRV) for CAN diagnosis, the prevalence of CAN after myocardial infarction (MI) is approximately 60%. In the CABG population, approximately 30% of patients have diabetes and/or MI. Therefore, we anticipate a CAN prevalence of at least 20%. Postoperative AKI incidence ranges from 12–36% in the literature. Assuming that at least 20% of our patients will be CAN-positive and that AKI incidence in CAN-positive patients will be at least 10% higher than in CAN-negative patients, with $\alpha = 0.05$ and $\beta = 0.2$, a minimum of 884 patients will be required.

INFORMED CONSENT AND VOLUNTEER INFORMATION FORM

(Physician's Explanation)

Dear Patient / Patient's Relative,

This study aims to investigate the effects of cardiovascular autonomic neuropathy (CAN) on acute kidney injury and outcome parameters in patients undergoing isolated coronary artery bypass surgery (CABG).

We recommend your participation in this study. However, it is entirely your choice whether or not to participate. Participation is voluntary. Before making your decision, we would like to inform you about the study. After reading and understanding this information, if you wish to participate, please sign this form.

Your participation in this study, which will be conducted at the Department of Anesthesiology and Reanimation at …… Hospital, is important for the success of the research.

If you agree to participate, Dr. …….. will review the data recorded after your surgery, and the findings will be documented. This research is not experimental, and its procedures do not pose any risk to you. You will not be charged any fees for participating in this study. No additional payment or insurance will be provided. Your medical information will be kept confidential.

You may refuse to participate. Participation is completely voluntary, and refusal will not affect your treatment in any way.

(Participant Declaration)

Dear Dr. ……, I have been informed about the medical research to be conducted at …… Hospital, and the above information has been explained to me. After this explanation, I have been invited to participate in this study as a volunteer.

If I participate, I understand that my personal information will be handled with strict confidentiality throughout the study. I trust that my data will be protected during the educational and scientific use of the study results. I will not bear any financial responsibility for the study procedures, nor will I receive any payment.

I understand that if any health problems arise, directly or indirectly, as a result of participating in this study, I will receive appropriate medical care without financial burden.

I understand that in case of a health issue during the study, I can contact Dr. …… at …… (work) or …… (mobile) at any time, or reach the Department of Anesthesiology and Reanimation at …… Hospital.

I understand that participation is voluntary and that I have not been pressured to join. Refusal to participate will not affect my medical care or my relationship with my physician.

I have fully understood all explanations. After careful consideration, I voluntarily accept the invitation to participate as a study subject.

A copy of this signed form will be provided to me.

Participant

Name, Surname:

Address:

Phone:

Signature:

Witness of the Discussion

Name, Surname:

Address:

Phone:

Signature:

Physician Who Discussed the Study

Name, Surname, Title:

Address:

Phone:

Signature: