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Association between transoesophageal echocardiography monitoring indicators and the incidence of postoperative acute kidney injury in coronary artery bypass grafting: a study protocol for a prospective multicenter cohort study

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ABSTRACT

Introduction Previous studies on transoesophageal echocardiography in coronary artery bypass grafting mainly focused on whether to change the surgical plan rather than improve the clinical prognosis. Currently, there are sparse studies on the relationship between transoesophageal echocardiography indicators and the prognosis of patients undergoing coronary artery bypass grafting. The primary aim of this study is to explore the association between transoesophageal echocardiography monitoring indicators the respiratory variability of inferior vena cava diameter, tricuspid annular plane systolic excursion and the incidence of acute kidney injury in coronary artery bypass grafting patients.

Methods and analysis We designed this prospective multicenter cohort study, which included approximately 150 adult patients (≥18 years) undergoing elective coronary artery bypass surgery. Different hospitals will be assessed to obtain information on the prevalence, risk factors, management strategies and outcomes in coronary artery bypass surgery. The cohort will be followed after the coronary artery bypass surgery period, up to 30 days after enrolment. The incidence of postoperative acute kidney injury and baseline data will be presented by descriptive statistics. We will use Freidman inspection and multivariable logistic regression to assess the association between transoesophageal echocardiography monitoring indicators and the incidence of acute kidney injury in coronary artery bypass grafting patients.

Ethics and dissemination The study has been approved by the ethics committee of Shandong Provincial Qianfoshan Hospital, China (approval number: YXLL-KY-2021(067)). This is an observational study that poses no risk to the patients. All participants will obtain informed consent according to the ethics committee before patient enrolment. Funding sources will have no influence on data handling, analyses or writing of the manuscript. The article is planned for submission in an international peer-reviewed journal.

Trial registration number NCT05139108.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective multicenter design allows us to assess geographical and interregional differences in the management strategies of coronary artery bypass grafting, which provide important data in this field and increase external validity.
⇒ The study has been planned and designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement, including a predefined statistical analysis plan, prespecified variables and outcomes of interest, thereby increasing the internal validity and transparency of the study.
⇒ Inherent limitations exist due to the observational design including risk of missing data, lost to follow-up and incomplete data collection, which may lower the precision of the data and introduce bias.
⇒ The multifactorial nature of acute kidney injury makes this study prone to residual confounding.

INTRODUCTION

Previous studies on transoesophageal echocardiography (TEE) mainly focused on whether to change the surgical plan instead of improving the clinical prognosis.[1 2] Currently, there are sparse studies on the evaluation of prognosis, which have low efficacy and inconsistent conclusions.[3–5] Acute kidney injury (AKI) is the most common postoperative complication of coronary artery bypass grafting (CABG) surgery, and is independently associated with hospitalisation and long-term mortality.[6] Among CABG patients, AKI, in addition to operation-related factors, is associated to renal perfusion.[7] These patients often have serious coronary multivessel lesions or myocardial infarction, or right heart dysfunction, which can cause

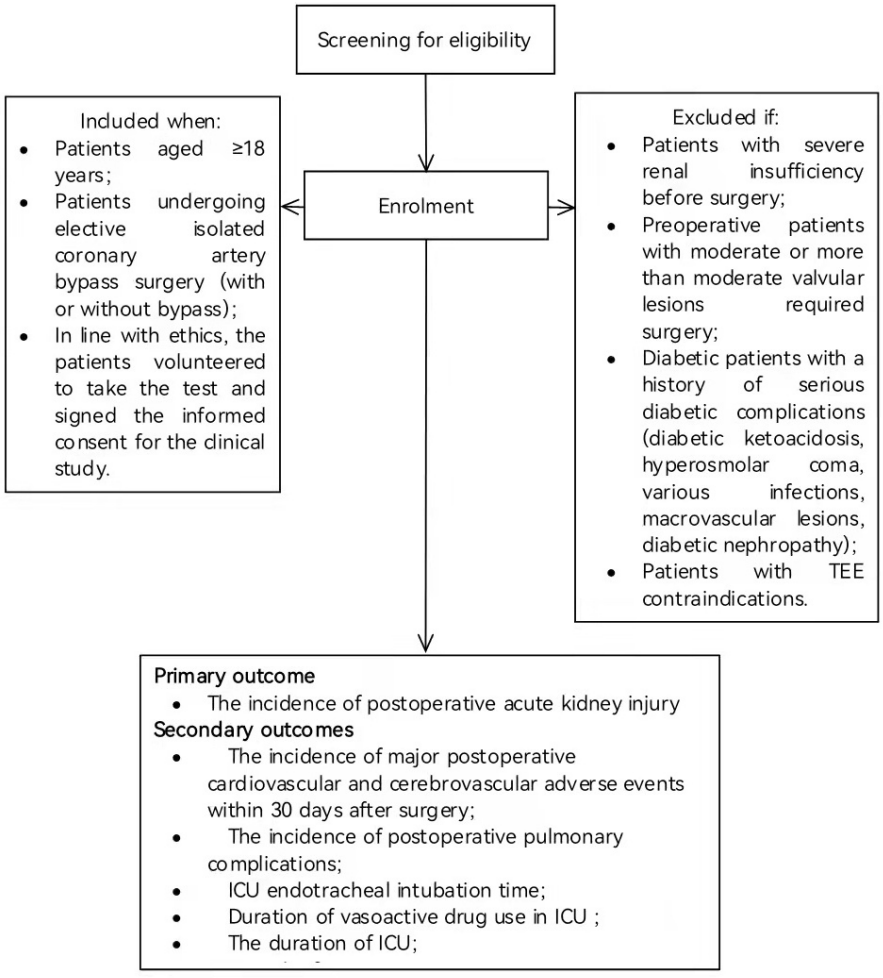

Figure 1 Study flow chart of patient recruitment. ICU, intensive care unit; TEE, transoesophageal echocardiography.

the system obstacle of regurgitation of the inferior vena cava (IVC) and kidney blood stasis, Inappropriate fluid management will affect kidney blood perfusion. These may be the reasons for the renal injury. Therefore, appropriate volume status plays an important role in maintaining right heart function and renal perfusion. What indicators can we use to quickly and effectively evaluate the patient's volume status and monitor the patient's right heart function?

In recent years, many studies have confirmed that the respiratory variability of IVC diameter (ΔIVC) measured by TTE has a good correlation with the volume status of patients on mechanical ventilation, which has a high diagnostic value for predicting the fluid responsiveness of such patients, and it also can be used to guide fluid management.[8–10] However, a few studies have been reported using TEE measurements of ΔIVC to assess volume status or guide fluid management in patients undergoing cardiac bypass surgery. In addition, previous studies have confirmed that tricuspid annular plane systolic excursion (TAPSE) measured by TTE is independently associated with AKI in intensive care unit (ICU) patients and can predict the occurrence of AKI in such patients.[11 12] However, TAPSE monitored by TEE has not been reported in this aspect. Can ΔIVC and TAPSE predict the incidence of AKI and major cardiovascular and cerebrovascular adverse events among CABG patients?

Therefore, we designed this prospective multicenter cohort study to investigate the validity and guidance of ΔIVC and TAPSE in CABG, so as to alleviate AKI, protect and improve patients' renal function, reduce postoperative mortality and incidence of major postoperative cardiovascular and cerebrovascular adverse events, and improve the clinical prognosis of patients undergoing such surgery.

Objectives

- To explore the association between TEE monitoring indicators ΔIVC, TAPSE and the incidence of AKI in CABG patients.
- To investigate the effectiveness and guiding significance of TEE monitoring in CABG.

METHODS AND ANALYSIS

Study design

This is a prospective multicenter cohort study. This study was approved by the Ethics Committee of Qianfoshan

Hospital of Shandong Province and the Ethics Committee of Zibo Central Hospital. This study protocol is conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Study setting

This study will be performed in Shandong Provincial Qianfoshan Hospital, Shandong University (located at No. 16 766 Jingshi Road, Jinan 250014, Shandong, China), and Zibo Central Hospital, Shandong University (located at No. 54 Gongqingtuan West Road, Zibo 255036, Shandong, China).

Patient and public involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Participants

From 6 September 2021 to 30 September 2023, participants provided the written informed consent, a total of 150 participants aged ≥18 years who are scheduled to accept elective CABG will be screened for eligibility by investigators in each individual site. Patients will be followed up within 30 days after CABG (see figure 1).

Eligibility criteria

Inclusion criteria

- Patients aged ≥18 years.
- Patients undergoing elective CABG (with or without bypass).
- In line with ethics, the patients volunteered signed the informed consent for the clinical study.

Exclusion criteria

- Patients with severe renal insufficiency before surgery.
- Patients with moderate or more than moderate valvular lesions required surgery.
- Diabetic patients with a history of serious diabetic complications (diabetic ketoacidosis, hyperosmolar coma, various infections, macrovascular lesions, diabetic nephropathy).
- Patients with TEE contraindications.

Exposure measures

After admission into the operation room, the participants will be continuously received the ECG monitor, non-invasive blood pressure monitoring, the pulse oxygen saturation monitor and the bispectral index of EEG monitoring (BIS). Radial artery catheterisation will be performed to monitor invasive artery blood pressure. Midazolam (0.05 mg/kg), etomidate (0.05–0.3 mg/kg), rocuronium (0.8 mg/kg) or cisatracurium besylate (0.2 mg/kg) and sufentanil (1–3 ug/kg) are administered for the general anaesthesia induction. General anaesthesia is maintained by a combination of intravenous and inhalation anaesthetics.

Ultrasound assessment consists of IVC ultrasound and RV functional ultrasound. The IVC diameter(D-IVC) was measured approximately 2 cm from the right atrium using a transgastric IVC LAX view (70°) in its M-mode cursor. Maximum and minimum D-IVC values over a single respiratory cycle were collected and the D-IVC variation (ΔIVC) calculated as the difference between the maximum and the minimum D-IVC value, normalised by the mean of the two values and expressed as a percentage. The main RV functional ultrasound indicator is TAPSE, which is acquired by mid-oesophageal four-chamber view (0°) and ME RV inflow-outflow view (60°) of M-mode cursor. All clinical and echocardiographic measurements were performed by three consecutive times and averaged at the time of T0, T1, T2, T3 (see table 1).

Outcome measures

Primary outcome

The incidence of postoperative AKI

Table 1 Time schedule of enrolment, exposure measures, and visits for participants

	Main study period							
	Screening	Enrolment	Exposure measures				Follow-up	
Time point	0	1	T0	T1	T2	T3	4	5
Informed consent	X							
Haemodynamic index			X	X	X	X		
Respiratory parameters			X	X	X	X		
Blood gas index			X	X	X	X		
Ultrasound indicators			X	X	X	X		
Blood test index			X	X	X	X		
Serum creatinine							X	X
Primary outcome							X	X
Secondary outcomes							X	X

T0: Before coronary artery bypass graft. T1: Before neutralisation of protamine. T2: 5~10 mins after neutralisation of protamine. T3: After the sternum closing. 4: 7 days after the surgery. 5: 30 days after the surgery.

Definition: AKI is defined as any of the following (not graded):[13 14]

- Increase in SCr by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours.
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
- Urine volume < 0.5 mL/kg/hours for 6 hours.

Secondary outcomes

- The incidence of major adverse cardiovascular and cerebrovascular events within 30 days after surgery

Definition: Major postoperative cardiovascular and cerebrovascular adverse events were defined as all-cause death, revascularisation of target vessels, nonfatal myocardial infarction, stroke or transient cerebral ischaemia, unstable angina requiring hospitalisation, and heart failure.

- The incidence of postoperative pulmonary complications

Definition: Postoperative pulmonary complications included pulmonary infection, pulmonary atelectasis, acute lung injury, respiratory failure after cardiac surgery within 30 days.

- ICU endotracheal intubation time

Definition: the endotracheal intubation time in ICU

- Duration of vasoactive drug use in ICU

Definition: The time of vasoactive drug use in ICU after cardiac surgery

- The duration of ICU

Definition: The icu stay time after cardiac surgery

- Length of stay

Definition: The duration of a single episode of hospitalisation

- Hospitalisation expenses

Definition: The cost of hospitalisation

Participant timeline

The potentially eligible participants will be screened according to the inclusion and exclusion criteria before surgery. After the written informed consent is obtained, the participants will be enrolled. From the beginning of general anaesthesia induction to the end of surgery, all of the relevant variables would be recorded by an independent investigator. The participants will be followed up and recorded from 1 d to 30 d after the surgery (see table 1).

Recruitment

One investigator of the study team will visit the patient at the day before surgery and will explain the study protocol. The patient will obtain informed consent and will be given enough time to read, assess and ask questions before deciding whether to participate or not. The patient will be assured that the quality of perioperative management will not be affected by their refusal to participate.

STATISTICAL METHODS

Sample size estimation

Previous studies showed an incidence of postoperative AKI of 5%–57.7% in patients undergoing CABG.[7 15] The sample size of this study was determined according to the events per variable (EPV) principle in multivariate Logistic regression analysis,[16] and 135 cases were estimated to be needed. Based on the calculation of 10% loss rate, the sample size was expanded to 150 cases.

Population to be analysed

We will present baseline data in the full cohort and stratified by whether patients developed AKI after CABG.

Continuous variables will be expressed as mean with SD or medians with IQRs, depending on normality determined with Shapiro-Wilk test. Categorical variables will be described as counts (percentages) and compared with χ^2 analysis or Fisher's exact test.

The prevalence of AKI The prevalence of AKI will be reported as the number of patients with a AKI-episode divided by the total number of patients.

Risk factors for AKI

We will use multivariate logistic regression analysis with adjusted ORs with 95% CIs to assess the crude and adjusted association between the following independent variables and AKI: age, gender, operation time, grafts number, cardiopulmonary bypass condition.

The association between ΔIVC and the incidence of AKI

We will use multivariate logistic regression analysis to assess the crude and adjusted cause-specific incidence ratios between ΔIVC and the incidence of AKI. We will adjust for the following important prognostic variables: age, gender, operation time, grafts number, cardiopulmonary bypass condition. The association between ΔIVC and the secondary outcomes will be presented descriptively.

Subgroup and sensitivity analyses

We will descriptively be stratified by gender, grafts number, cardiopulmonary bypass condition in patients who developed AKI or not after CABG. The data will be presented as distribution numbers and percentages. In addition, variation ΔIVC and other prespecified secondary outcomes will also be presented in the manuscript.

Handling of missing data

We expect a low degree of data missingness and any missingness will be reported. Missingness confined exclusively to the outcome[17] or for variables below 5% will lead to complete case analysis (exclusion of cases with missing data) in the prespecified analysis. If the degree of missingness is >5% of any variable in the predefined adjusted analyses, we will perform multiple imputation of missing variables assuming that data are missing at random unless otherwise stated in the statistical analysis.[17–19] The statistical analysis will be conducted in R4.0.2 and Free V1.3 statistical software.

Data collection

Data will be continuously collected in a case report form (CRF) from medical records and laboratory reports during the study period.

The entered data from CRF will be exported into an electronic database and stored as required by the data protection authorities.

Discontinuation of data collection

We will stop the daily registration if:

- The patient dies after cardiac surgery within 30 days.
- Patients are unwilling to follow up.

Study closure

When the 30-day follow-up period has ended for all included patients.

Data management

The local investigators are responsible for the data collection and their accuracy.

In addition, the local investigators will ensure the completeness of the CRF after the follow-up period. No analyses will be performed before data accuracy has been assured.

Study record retention

All research and relevant documents will be stored confidentially and securely for 10 years at the Department Of Anaesthesia and perioperative medicine, Qianfoshan Hospital, and Department of Anesthesiology, Zibo Central Hospital following the end of the study. The members of the Management Committee have access to stored data. On request, investigators can get access to data from their own unit.

Confidentiality

The obtained data and other information from included participants will be held in strict confidence by the investigators, research staff, and sponsoring institute.

No information or data concerning the study will be released by any unauthorised third party, without a prior written approval of the sponsoring institution. Authorised representatives from the sponsoring institution may inspect all documents and records required to be maintained by the investigator.

All laboratory specimens and reports that leave the site will be identified only by the Subject Identification (SIA) to ensure confidentiality.

Modification of the protocol

The study will be conducted according to the current version of the protocol. Any change in the protocol having impact on the scientific intent, study design, or results will be amended to the protocol.

Harms

This is a non-interventional study due to the observational study design and poses no risk to the patients. All the participation sites must obtain relevant approvals from national research committees according to national laws before patient enrolment.

Ethics and dissemination

The study has been approved by the ethics committee of Shandong Provincial Qianfoshan Hospital, China (approval number: YXLL-KY-2021(067)). This is an observational study that poses no risk to the patients. All participants will obtain informed consent according to the ethics committee before patient enrollment. Funding sources will have no influence on data handling, analyses or writing of the manuscript. The article is planned for submission in an international peer-reviewed journal.

DISCUSSION

This is a prospective multicenter cohort study aimed to investigate the association between TEE monitoring indicators and the incidence of postoperative AKI in CABG.

The TEE-AKI inception study have several strengths. The study has been planned and designed in accordance with the STROBE Statement,[20] including a predefined statistical analysis plan, prespecified variables and outcomes of interest, thereby increasing the internal validity and transparency of the study. The multicenter design allow us to assess geographical and interregional differences in management strategies of CABG, which provide important data in this field and increase external validity.

Inherent limitations exist due to the observational design including risk of missing data, lost to follow-up and incomplete data collection, which may lower the precision of the data and introducing bias. In addition, the multifactorial nature of AKI makes this study prone to residual confounding.

In conclusion, the TEE-AKI inception cohort study will provide important information about TEE monitoring in CABG, and the results will inform a future randomised clinical trial on the superior therapy in adult CABG patients with AKI.

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Contributors Study design: YW, BL. Screening, Enrolling participants, Data collection, Follow-up and Writing of the report: BL, HW. Management and Literature Search: ML, XS, LD. Statistical Analysis: YS, HF.

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Competing interests All participating researchers are obliged to declare any conflicts of interest or financial interest related to the study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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