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Postoperative plasma copeptin levels independently predict delirium and cognitive dysfunction after coronary artery bypass graft surgery

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ABSTRACT

Copeptin can reflect individual's stress state and are correlated with poor outcome of critical illness. The occurrence of postoperative delirium (POD) and cognitive dysfunction (POCD) is associated with worse outcome after coronary artery bypass graft (CABG) surgery. The present study aimed to investigate the ability of postoperative plasma copeptin level to predict POD and POCD in patients undergoing CABG surgery. Postoperative plasma copeptin levels of 108 patients were measured by an enzyme-linked immunosorbent assay. It was demonstrated that plasma copeptin levels were substantially higher in patients with POD than without POD (1.8 ± 0.6 ng/mL vs. 1.1 ± 0.3 ng/mL; $P < 0.001$) and in patients with POCD than without POCD (1.9 ± 0.6 ng/mL vs. 1.1 ± 0.4 ng/mL; $P < 0.001$). Plasma copeptin level and age were identified as independent predictors for POD [odds ratio (OR), 67.386; 95% confidence interval (CI), 12.031–377.426; $P < 0.001$ and OR, 1.202; 95% CI, 1.075–1.345; $P = 0.001$] and POCD (OR, 28.814; 95% CI, 7.131–116.425; $P < 0.001$ and OR, 1.151; 95% CI, 1.030–1.285; $P = 0.003$) using a multivariate analysis. For prediction of POD, the area under receiver operating characteristic curve (AUC) of the copeptin concentration (AUC, 0.883; 95% CI, 0.807–0.937) was markedly higher than that of age (AUC, 0.746; 95% CI, 0.653–0.825; $P = 0.020$). For prediction of POCD, the AUC of the copeptin concentration (AUC, 0.870; 95% CI, 0.792–0.927) was markedly higher than that of age (AUC, 0.735; 95% CI, 0.641–0.815; $P = 0.043$). Thus, postoperative plasma copeptin level may be a useful, complementary tool to predict POD and POCD in patients undergoing CABG surgery.

Introduction

Postoperative delirium (POD) and cognitive dysfunction (POCD) are the common complications after cardiac surgery including coronary artery bypass graft (CABG) surgery [7,8,18,28]. The occurrences of POD and POCD are associated with multiple adverse effects, such as prolonged hospital stay, increased health care cost and high mortality rate [9,12,14,24]. Despite the numerous studies, the pathophysiology of POD and POCD remains poorly understood. The accumulating evidences show that the stress response induced by surgical stimuli might play an important role in the pathogenesis of POD and POCD [1,13,17,25].

Copeptin is the C-terminal fragment of provasopressin and is presumably co-secreted with arginine vasopressin from the hypothalamus [10,26]. Copeptin concentrations in plasma increase as a response of physiological stress and have been shown to have prognostic value in several disease entities, such as cardiovascular disease, head injury, stroke, pulmonary disease and shock [2,3,15,16,19]. Copeptin could, therefore, be a marker for POD and POCD in patients undergoing cardiac surgery. The present study aimed to investigate the ability of postoperative plasma copeptin level to predict POD and POCD in patients undergoing CABG surgery.

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Materials and methods

Study population

This study included these patients aged 18 years and above who underwent elective CABG surgery from April 2010 to May 2013 in the Second Affiliated Hospital, Wenzhou Medical University and the Fourth Affiliated Hospital, Haerbin Medical University. Exclusion criteria included Mini-Mental State Examination score <24 before surgery, previous psychiatric disorder, previous cardiothoracic surgery, any severe visual or auditory disorders, concomitant surgery other than CABG, unavailable biomarker measurements, refusal of participation, and unable to speak or understand Chinese. Patients were included in this study after they or their relatives provided written informed consent. This protocol was approved by the Ethics Committees of the Second Affiliated Hospital, Wenzhou Medical University and the Fourth Affiliated Hospital, Haerbin Medical University before implementation.

Clinical assessment

On admission, we recorded the demographics such as age, gender and body mass index, previous medical comorbidities such as myocardial infarction, arrhythmia, chronic obstructive pulmonary disease and stroke, and concomitant cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, chronic smoking and alcoholism. Chronic smoking was defined as smoking of >20 cigarettes per day within 1 month. Alcoholism was defined as consumption of an equivalent of 150 mL of alcohol per week.

Preoperative transthoracic echocardiography was performed. A 16-segment left ventricular wall motion index score was determined based on the American Society of Echocardiography method [27]. The left ventricular ejection fraction was calculated using the biplane method of disks formula. Impaired left ventricular systolic function was defined as either a left ventricular ejection fraction <40% or a ventricular wall motion index score >1.8 [23]. Preoperative Canadian Cardiac Society (CCS) classification and New York Heart Association (NYHA) classification and European System for Cardiac Operative Risk Evaluation score (EuroSCORE) were determined by the first cardiology specialist to examine the patient.

We recorded perioperative possible confounding factors including duration of anesthesia, dose of etomidate (0.1–0.4 mg/kg) during induction, use of penehyclidine (1.0 mg), atropine (0.3–1.0 mg) and dexamethasone (10 mg) during anesthesia, duration of surgery, surgery under cardiopulmonary bypass, number of bypass grafts, and amount of blood transfusion.

Delirium evaluation

Delirium was evaluated using the Confusion Assessment Method for the intensive care unit (CAM-ICU) [4,5]. CAM-ICU scores are determined using a diagnostic algorithm consisting of four features: (1) acute and fluctuating changes in mental status, (2) inattention, (3) disorganized or incoherent thinking, and (4) an altered level of consciousness. CAM-ICU scores are considered to indicate delirium if Features 1 and 2 are present and either Feature 3 or 4 is present. During the study phase, patients were assessed for delirium twice daily until the seventh postoperative day.

Neurocognitive evaluation

Neuropsychological evaluation was performed 1 d before and one week after surgery. In total, a battery of 12 neuropsychological tests was used that assessed a range of cognitive functions including attention, memory and executive function. The presence of POCD was defined according to the method used in the ISPOCD1 studies [20]: we calculated the standard deviation (SD) of the differences in neuropsychological test results conducted within the same time interval from 50 age- and sex-matched healthy individuals (control group). For patients, the differences between baseline (preoperative) scores and scores at one week postoperatively were divided by the control group SD to obtain a Z score for each individual test. Patients were defined as have POCD if they had a Z score greater than 1.96 on two or more tests.

Immunoassay methods

Blood samples were obtained between 7 and 8 a.m. on the first postoperative day. Samples were placed on ice, centrifuged at $3000 \times g$, and plasma aliquoted and frozen at $-70\,^{\circ}C$. The concentrations of copeptin in plasma were analyzed by enzyme-linked immunosorbent assay using commercial kits (Phoenix Pharmaceuticals, Belmont, CA) in accordance with the manufactures' instructions. The person carrying out the assays was completely blinded to the clinical information.

Statistical analysis

Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The results were reported as counts (percentage) for the categorical variables, and mean ± standard deviation for the continuous variables. Comparisons were made by using (1) chi-square test or Fisher exact test for categorical data, and (2) Student's t test for continuous variables. The effect of plasma copeptin levels on the occurrence of POD and POCD was assessed with the use of multivariate logistic regression analyses. Initially, baseline and perioperative variables were evaluated for univariate association with POD and POCD. Variables that were significant in univariate analyses were included in a multivariate logistic regression model to determine the risk-adjusted predictors of POD and POCD with odds ratio (OR) and 95% confidence interval (CI). The receiver operating characteristic (ROC) curves were used to determine the best threshold of copeptin values to predict POD and POCD with calculated area under curve (AUC) and 95% CI. A combined logistic-regression model was configured to show whether the combination of age and copeptin improved the additive benefit. A 2-tailed probability value of <0.05 was considered as statistically significant.

Results

Patients characteristics

This study eventually included one hundred and eight patients. This group of patients included 83 men and 25 women and had a mean age of 63.0 ± 7.9 years and a mean body mass index of 26.0 ± 2.5 kg/m^2. 39 patients (36.1%) had previous myocardial infarction; 23 patients (21.3%), arrhythmia; 5 patients (4.6%), chronic obstructive pulmonary disease; 11 patients (10.2%), stroke; 65 patients (60.2%), hypertension; 28 patients (25.9%), diabetes mellitus; 42 patients (38.9%), hypercholesterolemia; 16 patients (14.8%), alcoholism; 45 patients (41.7%), chronic smoking; 25 patients (23.1%), impaired left ventricular systolic function; 89 patients (82.4%), CCS classification >I; 83 patients (76.9%), NYHA classification >I. The mean EuroSCORE was 2.7 ± 1.0; the mean duration of anesthesia, 5.2 ± 1.3 h; the mean dose of etomidate during induction, 0.21 ± 0.08 mg/kg. During anesthesia, 22 patients (20.4%), 12 patients (11.1%) and 40 patients (37.0%) used penehyclidine, atropine and dexamethasone respectively. The mean duration of surgery was 4.4 ± 1.0 h. 47 patients (43.5%) underwent surgery under cardiopulmonary bypass. 8 patients (7.4%)