Postoperative Adverse Cardiovascular Events Associated with Leptin and Adverse Age After Elective Major Non-Cardiac Surgery: An Asian Single-Center Study

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Background: The postoperative adverse cardiovascular events (PACE) after surgery can result in prolonged length of stay and poorer prognosis. The purpose of this Asian single-center study was to investigate the potential predicative role of leptin for PACE in elderly patients undergoing major non-cardiac surgery.

Material/Methods: The patients in the study were prospectively recruited from a series of elderly patients (≥60 years) undergoing elective major non-cardiac surgery (≥2 hours) in our hospital from June 2013 to June, 2016. The demographic and clinical data and the preoperative serum biomarkers of each participant were recorded in details. Suspected PACE were assessed by the same experienced expert based on clinical, blood, and other accessory tests. The univariate and multiple logistic regression analyses were plotted to evaluate the potential independent predictive factors for PACE.

Results: A total of 270 elderly patients (145 males and 125 females), undergoing major elective non-cardiac surgery, were finally enrolled in this study. Older age, higher revised cardiac risk index score, higher levels of systolic blood pressure, B-type natriuretic peptide and leptin, the preoperative medication of beta blocker and lipid-lowering agents were positive predictors of PACE by univariate analyses ($p<0.05$). Our results indicated that preoperative leptin level (OR 1.84, 95% CI 1.08–3.42; $p=0.015$) and advanced age (OR 0.24, 95% CI 0.09–0.94; $p=0.041$) were significantly associated with the occurrence of PACE by multiple logistic regression analyses.

Conclusions: Preoperative serum leptin level and advanced age were two independent risk factors for PACE among elderly patients undergoing elective major non-cardiac surgery.

MeSH Keywords: **Aged • Postoperative Care • Surgery, Computer-Assisted**

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Background

Cardiovascular complications have been considered significantly associated with increased morbidity and mortality in patients after non-cardiac surgery, especially in elderly patients [1]. The postoperative adverse cardiovascular events (PACE), including arrhythmias and myocardial infarction, can result in prolonged length of stay and poorer prognosis. The mortality rate can reach as high as 15–25% in those patients who suffer a postoperative myocardial infarction [2,3]. Preoperative risk assessment tools and useful biomarkers are important strategies for risk stratification of postoperative major cardiovascular complications. Previous studies have indicated some clinical risk factors for the estimation of cardiovascular events risk [4]. B-type natriuretic peptide (BNP) and N-terminal fragment BNP (NT-proBNP) are reported as appropriate predicative factors for atrial fibrillation and postoperative cardiopulmonary complications in elderly patients undergoing thoracic surgery [5,6]. Inflammatory activity-related biomarkers, e.g., interleukin 6 (IL-6) and C-reactive protein (CRP), have also been reported associated with cardiovascular disease [7]. Leptin, a peptide hormone mainly produced by adipose tissue, has been reported by recent studies to be linked with some cardiovascular risk factors and short-term major adverse cardiac events in patients with coronary artery disease [8]. The purpose of this study was to investigate potential predicative factors for PACE in elderly patients undergoing major non-cardiac surgery.

Material and Methods

Patients and methods

This single-center study protocol was approved by the Medical Institutional Ethics Committee of Jiangsu province and Taizhou People's Hospital. The patients in the study were prospectively recruited from a series of elderly patients (≥60 years) undergoing elective major non-cardiac surgery (≥2 hours) in our hospital from June 2013 to June, 2016. Informed consent was obtained from the participants. Upon entering the study, enrolled patients underwent preoperative evaluations and the detailed information was collected including past medical history; physical and accessory examination was recorded. Extensive assessment for cardiovascular diseases was also conducted through clinical examination, body measurements, accessory examination, and serum biomarker analyses. Chest x-rays and electrocardiogram (ECG) were carried out as the routine inspection before the surgery for all enrolled patients. The demographic and clinical data of each participant was recorded in details. The revised cardiac risk index (RCRI) was also assessed according to the accrued risk value between 0 and 6 as reported by previous studies [9].

Blood sampling and laboratory examinations

To carry out the laboratory examinations, preoperative fasting venous blood samples were obtained. Serum aliquots were separated from blood samples via centrifugation and then stored at –70°C until processed. Serum biomarkers including adiponectin, leptin, CRP, IL-6, MB isoenzyme of creatinine kinase (CK-MB), BNP, cardiac troponin T (cTnT), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured from the obtained samples. HDL-C and LDL-C expressions were measured via ultracentrifugation. Serum concentrations of CRP, IL-6, CK-MB, cTnT, adiponectin, and leptin (R&D Systems, Minneapolis, MN) were all measured by the method of enzyme linked immunosorbent assay (ELISA). Serum BNP concentration measurements were carried out with chemiluminescent enzyme immunoassay kit (Biosite Incorporated, San Diego, CA, USA).

Follow-up

The follow-up was obtained by chart review at hospitalization or outpatient clinics. Suspected PACE were assessed by the same experienced expert based on clinical, blood, and other accessory tests. The primary end-point was set as the occurrence of PACE, mortality or 30-day follow-up after the operation. Adverse cardiovascular events included myocardial infarction, acute coronary syndrome, ischemic heart disease, ventricular fibrillation, cardiac arrest, pulmonary edema, shock, heart failure, acute pulmonary embolism. The detailed definitions of these adverse events were made as per the descriptions used by previous studies with Asian standard [10,11].

Statistical analysis

Routine statistical analysis was performed on SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) and data were plotted by Graph Pad prism 5.0 (GraphPad Software, Inc., San Diego, CA, USA). Results are expressed as mean ± standard error (SE) and number with percentage (n,%) for continuous and categorical variables respectively. Mann-Whitney U-test, Student's t-test, chi-square test or Fisher exact test were utilized for data analysis appropriately. The univariate and multiple logistic regression analyses were plotted to evaluate the potential independent predictive factors for PACE. All statistical tests were bilateral probability and $p<0.05$ was considered significant.

Results

Patients' characteristics

A total of 270 elderly patients (145 males and 125 females) undergoing major elective non-cardiac surgery were finally

enrolled from June 2013 to June, 2016. The mean age of all the patients was 66.9 years with a mean body mass index (BMI) of 23.4 kg/m^2. The detailed characteristics of the study patients, with or without PACE, are shown in Table 1. The occurrence of PACE was observed in a close correlation with an older age, a higher BMI, RCRI score, and systolic blood pressure (SBP). In contrast, the gender, American Society of Anesthesiologists (ASA) physical status, heart rate, diastolic BP, types of surgery, estimated blood loss, duration of surgery, and anesthesia were all inversely associated with PACE. Those patients in the presence of comorbidities (coronary artery disease, ischemic heart disease, and heart failure) were more likely to suffer PACE after major surgery. Moreover, the preoperative usage of medication (beta blocker and lipid-lowering medication) might seemingly reduce the incidence of PACE.

Preoperative biomarkers and PACE

Table 2 shows the relationship between the concentrations of preoperative biomarkers and occurrence of PACE. The results revealed that higher levels of BNP, cTnT, and CRP were significantly associated with the occurrence of PACE. Analysis of CK-MB levels separately in patients showed higher levels in PACE patients than non-PACE patients. It is important to note that leptin expression in patients with PACE was far higher than those without PACE in our study population. However, no significant differences were observed between PACE and the concentrations of IL-6, HDL-C, LDL-C, or adiponectin.

Risk factors and PACE

As shown in Table 3, univariate analysis of each component was first conducted to investigate risk factors associated with PACE. Older age, higher RCRI score, higher levels of systolic BP, BNP, and leptin, preoperative beta blocker and lipid-lowering medications were positive predictors of PACE. However, the differences were not statistically significant by the final multivariate logistic regression analysis except age and leptin level. Our results indicated preoperative leptin level (OR 1.84, 95% CI 1.08–3.42; p=0.015; Table 3) and advanced age (OR 0.24, 95% CI 0.09–0.94; p=0.041; Table 3) as two independent risk factors for PACE.

Discussion

In the present study, we showed that an advanced age and elevated serum preoperative leptin level were two independent predictive risk factors for PACE in elderly patients undergoing major non-cardiac surgery. Obesity is recognized as a well-established predicative factor for cardiovascular events by previous studies [12], and our results from univariate analysis also suggested that a higher BMI was significantly associated with PACE. However, our final multivariate analysis didn't suggest it had a prognostic role for PACE. We considered that the differences in definitions of obesity between Asian and WHO criteria might lead to different conclusions. The RCRI score, a widely used tool for cardiovascular risk assessment, was shown not to be associated with PACE prediction probably due to its low predictability in our cohort of elderly patients.

BNP is secreted by the myocardium stimulated by inflammation, ischemia, or myocardial stretch [13]. Previous studies by Lucio et al. [14] have indicated a postoperative BNP elevation as an independent predictor of cardiopulmonary complications in patients undergoing major pulmonary resections; which was not quite in accordant with our results. Studies by Andersson et al. [15] have shown that β-blocker medication was significantly correlated with reduced risk of 30-day major cardiovascular adverse events among patients with ischemic heart disease after non-cardiac surgery. Their conclusion was in accordance with our results from the univariate analysis; however, there was no positive result by multivariate analysis.

Preoperative statin therapy can decrease the mortality among patients undergoing isolated valve surgery [16] or protect patients with stable coronary artery disease from major adverse cardiovascular and cerebrovascular events after non-cardiac surgery [17]. However, our final analysis didn't suggest a positive correlation between preoperative lipid-lowering medication and PACE as expected. Prior coronary artery disease and advanced age are independent risk factors for major cardiovascular and cerebrovascular complications for patients who underwent head or neck surgery [18]. In our series, advanced age was also recognized as an important risk factor for PACE.

The definitive role of leptin in cardiovascular events still remains unclarified until now. Previous studies have achieved controversial conclusions concerning the role of leptin in cardiovascular system with both beneficial and detrimental effects [19]. Some studies have shown that leptin can be induced by proinflammatory cytokines after acute myocardial infarction and exert cardio-protective effects, thereby improving prognosis [20]. Previous analysis conducted in patients with coronary artery disease showed that elevated plasma leptin level was significantly correlated with impaired left ventricular filling pattern [21], increased heart failure morbidity, and cardiac death [8]. A prospective study carried out in patients with atherosclerosis indicated leptin was an independent predicative factor for adverse cardiovascular events [22]. Leptin has a prognostic power in the coronary artery disease patients due to its potential proatherogenic effects and confounding with other proatherosclerotic factors [23]. As reported by previous studies conducted in experimental mice models, leptin also played a critical role in injured tissues restoration after acute myocardial infarction by improving systolic function, left

Table 1. Characteristics of patients with or without PACE.

Parameters	PACE				p-Value
	Yes		No		
Number (n)	56		214		–
Age (year)	68.6±7.8		66.4±5.7		0.019*
Sex (n,%)					
Male	36	(64.3%)	109	(50.9%)	
Female	20	(35.7%)	105	(49.1%)	0.074
ASA physical status					
I–II	37	(66.1%)	152	(71.0%)	
III–IV	19	(33.9%)	62	(29.0%)	0.471
RCRI					
I	26	(46.4%)	120	(56.1%)	
II	22	(39.3%)	85	(39.7%)	
III	8	(14.3%)	9	(4.2%)	0.019*
Comorbidities					
Diabetes mellitus	8	(14.3%)	30	(14.0%)	0.959
Anemia	5	(8.9%)	19	(8.9%)	0.991
COPD	3	(5.4%)	18	(8.4%)	0.412
Peripheral artery disease	2	(3.6%)	7	(3.3%)	0.947
Cerebrovascular disease	4	(7.1%)	20	(9.3%)	0.560
Atrial fibrillation	8	(14.3%)	24	(11.2%)	0.589
Coronary artery disease	11	(19.6%)	20	(9.3%)	0.041*
Ischemic heart disease	13	(23.2%)	19	(8.9%)	0.005*
Heart failure	15	(26.8%)	24	(11.2%)	0.007*
Myocardial infarction	3	(5.4%)	12	(5.6%)	0.898
BMI (kg/m^2)	24.3±3.3		23.2±2.8		0.012*
Heart rate	79.6±24.7		74.5±28.3		0.219
SBP (mmHg)	127.8±35.4		116.5±29.4		0.015*
DBP (mmHg)	72.6±19.8		68.3±20.1		0.154
Preoperative medication					
Beta blocker	7	(12.5%)	52	(24.3%)	0.045*
ACEI/ARB	11	(19.6%)	51	(23.8%)	0.433
Calcium channel blocker	10	(17.9%)	39	(18.2%)	0.863
Lipid-lowering medication	8	(14.3%)	60	(28.0%)	0.035*

Table 1 continued. Characteristics of patients with or without PACE.

Parameters	PACE		p-Value
	Yes	No	
Types of surgery			
Abdominal	16 (28.6%)	55 (25.7%)	
Orthopedic	21 (37.5%)	86 (40.2%)	
Intrathoracic	6 (10.7%)	26 (12.1%)	
Urologic	8 (14.3%)	23 (10.7%)	
Other	5 (8.9%)	24 (11.2%)	0.910
Duration of surgery (min)	170.1±50.4	163.8±44.5	0.360
Duration of anesthesia (min)	185.2±58.8	179.3±49.8	0.448
Estimated blood loss (ml)	265.3±187.9	287.1±167.5	0.399

PACE – postoperative adverse cardiovascular events; ASA – American Society of Anesthesiologists; RCRI – revised cardiac risk index; COPD – chronic obstructive pulmonary disease; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker. The p-values were calculated by chi-square test, Fisher exact test, Student's t-test or Mann-Whitney U-test; * p value <0.05. The increased incidence of PACE was observed in a close correlation with an older age, a higher RCRI score, SBP, higher incidence of comorbidities (coronary artery disease, ischemic heart disease, and heart failure) and lower medication rates (beta blocker and lipid-lowering medication).

Table 2. Preoperative laboratory parameters of patients with or without PACE.

Laboratory parameters	PACE		p-Value
	Yes	No	
Number (n)	56	214	–
BNP (pg/mL)	39.3±25.7	26.2±19.7	0.000*
cTnT (ng/L)	12.1±6.6	9.6±4.3	0.001*
CRP (mg/L)	10.2±8.5	7.1±5.2	0.001*
IL-6 (pg/mL)	20.3±27.4	18.2±21.1	0.535
CK-MB (U/L)	14.4±7.5	9.5±4.8	0.000*
HDL-C (mg/dL)	1.4±0.3	1.3±0.4	0.820
LDL-C (mg/dL)	2.2±0.7	2.1±0.6	0.285
Creatinine (mg/dL)	1.8±1.3	1.5±1.0	0.063
Leptin (ng/mL)	12.4±13.5	4.8±5.1	0.000*
Adiponectin (µg/mL)	9.5±5.4	8.3±6.8	0.222

PACE – postoperative adverse cardiovascular events; BNP – B-type natriuretic peptide; cTnT – cardiac troponin T; CRP – C-reactive protein; IL-6 – interleukin-6; CK-MB – MB isoenzyme of creatinine kinase; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol. The p-values were calculated by Student's t-test or Mann-Whitney U-test; * p value <0.05. Higher expressions of BNP, cTnT, CRP, CK-MB and leptin were significantly associated with the occurrence of PACE.

Table 3. Univariate and multiple logistic regression analysis for PACE after major elective non-cardiac surgery.

Variables	Univariate		Multivariate	
	OR (95%CI)	*p* Value	OR(95%CI)	*p* Value
Age	3.14 (1.21–7.84)	0.022*	0.24 (0.09–0.94)	0.041*
RCRI	0.39 (0.11–0.79)	0.019*	1.44 (0.48–3.27)	0.578
Coronary artery disease	1.03 (0.95–1.22)	0.133		
Ischemic heart disease	1.37 (0.45–5.14)	0.651		
Heart failure	2.43 (0.68–9.41)	0.097		
BMI	0.97 (0.83–1.12)	0.387		
SBP	1.64 (1.01–2.67)	0.024*	1.34 (0.85–2.55)	0.089
Beta blocker medication	0.47 (0.15–0.64)	0.011*	0.79 (0.55–1.34)	0.316
Lipid-lowering medication	0.31 (0.09–0.94)	0.034*	1.98 (0.71–6.01)	0.192
BNP	3.14 (1.68–5.37)	0.008*	1.61 (0.44–5.32)	0.431
cTnT	0.36 (0.09–1.37)	0.187		
CRP	1.32 (0.49–3.97)	0.448		
CK-MB	1.67 (0.55–4.37)	0.416		
Leptin	4.41 (2.47–8.17)	0.001*	1.84 (1.08–3.42)	0.015*

PACE – postoperative adverse cardiovascular events; RCRI – revised cardiac risk index; BMI – body mass index; SBP – systolic blood pressure; BNP – B-type natriuretic peptide; cTnT – cardiac troponin T; CRP – C-reactive protein; CK-MB – MB isoenzyme of creatinine kinase; CI – confidence interval; OR – odds ratio; * *p* value <0.05. Preoperative leptin level and advanced age were two independent risk factors for PACE.

ventricular remodeling [24] and exhibiting severe cardiac dysfunction [25]. Another study indicated elevated serum leptin level closely correlated with increased incidence of myocardial infarction [26]. Our results also suggested that serum leptin level was related to the occurrence of PACE in elderly patients undergoing major elective non-cardiac surgery with unknown etiology. These converse conclusions suggest that different characteristics of study cohorts may result in different relationships between leptin expressions and clinical outcomes. The possible profibrotic role in the myocardium may be a possible pathway by which leptin exerts harmful effects in heart disease related to myocardial fibrosis [15]. Recent studies have also revealed the complex role of leptin in PACE and "leptin resistance" might be one of the important mechanisms [27]. Circulating leptin can play a significant role in the prevention of toxic lipid accumulation [28]; however, dysregulated leptin concentrations are involved in metabolic disorders and lead to the poor prognosis in subjects [29]. Furthermore, the cardioprotective effects of leptin in patients after cardiac surgeries, and the putative association between leptin and PACE still remain uncertain with limited evidence [30].

Conclusions

In our opinion, preoperative serum leptin level and advanced age are two independent risk factors for PACE among elderly patients undergoing major non-cardiac surgery. As for those patients with advanced age and elevated serum leptin levels, more careful evaluation and attention are recommended to prevent PACE. In addition, more prospective multi-center investigations are required to clarify the prognostic value of leptin in the prediction of PACE.

Conflict of interests

None.

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