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Preoperative Leukocyte Counts Increase Risk of Adverse Outcomes in Obese Patient Undergoing Cardiac Surgery

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Abstract

Obesity is a chronic inflammatory state associated with increased postoperative morbidity in patients undergoing cardiac surgery. In this study, we sought to determine whether the white blood cell (WBC) response may be an additional predictor for postoperative morbidities in obese patients undergoing cardiac surgery. A total of 1,171 consecutive patients who underwent cardiac surgery were retrospectively reviewed. Patients were divided into three groups based on their body mass index (BMI): non-obese (BMI < 30 kg/m^2), obese (BMI 30-34.9 kg/m^2) and severely obese (BMI ≥ 35 kg/m^2). We used serial WBC count as an index of inflammation. Postoperative infection rate and postoperative hospital and intensive care unit (ICU) lengths of stay (LOS) were the primary endpoints. Obese and severely obese patients had significantly higher preoperative WBC counts and greater changes from the baseline at 24 h post-operation ($P < 0.01$). Obese and severely obese patients had significantly higher postoperative infection rate ($P < 0.01$). The postoperative LOS was significantly longer in severely obese patients ($P = 0.03$), and the ICU LOS was significantly longer in severely obese patients compared to non-obese patients ($P = 0.02$). Using logistic regression analysis, we identified the preoperative WBC count as an independent predictor for longer ICU stay and higher postoperative infection rate, and changes in WBC from preoperative baseline as a predictor for postoperative length of hospital stay in addition to BMI. Obese patients have increased postoperative morbidity after cardiac surgery. In addition to BMI, preoperative WBC count and the increase in WBC from the baseline in the immediate postoperative period are independent predictors for postoperative adverse outcomes.

Key Words: adverse outcome, cardiac surgery, inflammation, leukocyte, obesity

Introduction

During the past 40 years, there has been a dramatic increase in obesity worldwide. In 2014, 11% of adult men and 15% of adult women were obese as defined by body mass index (BMI) ≥ 30[1].

Obesity is associated with a variety of metabolic and hormonal dysfunctions that may lead to the development of diabetes mellitus, hypertension, dyslipidemia and coronary artery disease. Obesity has been considered a chronic inflammatory state (3, 13, 16). Even "healthy" obese populations have been reported to be associated with higher levels of C-reactive protein (CRP), proinflammatory cy-

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tokines including interlukin (IL)-6, IL-12, IL-18, tumor necrosis factor-α (TNF-α), and white blood cell (WBC) counts (2, 13, 22). Elevations of these inflammatory markers have been associated with increased cardiovascular risk (15).

Several retrospective studies confirmed that obese patients (BMI $\geq$ 35) undergoing cardiovascular surgery have higher rates of harvest site and deep sternal wound infections, are more likely to develop renal failure, and tend to have longer mechanical ventilation days, postoperative stays, and more frequent intensive care unit (ICU) readmission (11, 24). Another retrospective study concluded that morbidly obese patients (BMI > 40) caused nearly 60% greater observed mortality in patients underwent surgery for coronary artery disease (7). Conversely, some studies found an inverse relationship between obesity and adverse surgical outcomes, which is referred to as the "obesity paradox" (12, 17, 20, 21).

Because the BMI is neither a measure of body fat distribution, nor does it discriminate between fat mass and lean mass, we postulate that adipose tissue-related chronic inflammatory state in obese individuals might be the cause of increased post-surgical risk. We tested this hypothesis in obese patients undergoing cardiac surgery. We used preoperative leukocyte counts and the rise in WBC from the preoperative baseline as indices of inflammation. The rate of postoperative wound infection, mechanical ventilator days, and postoperative and ICU lengths of stay (LOS) were used as primary outcome measures.

Materials and Methods

Patients

With approval from the Duke University Medical Center Institutional Review Board, we reviewed the electronic medical database of all patients who were admitted to the cardiothoracic surgical intensive care unit (CTICU) of Duke University Medical Center between July 1, 2005 and June 30, 2007. Only patients who had undergone elective cardiac surgery were included in this study. The exclusion criteria included age less than 18 years or greater than 90 years, metastatic cancer, hematologic malignancies, solid organ or bone marrow transplantation, major trauma with shock, evidence of active infection before surgery, and history of chemotherapy or radiotherapy.

Data Collection

We recorded the patients' sex, age and preexisting medical comorbidities. We also recorded preoperative WBC counts (WBC_{pre}) and WBC count during the immediate postoperative period (WBC_{post} within 24 h of surgery). If there were more than one value within the period, all values were averaged. The outcome measures included postoperative LOS, LOS in the ICU, duration of mechanical ventilation, reintubation rate, ICU readmission rate within 14 days and postoperative infection rate. A patient was considered to have postoperative infection if he or she developed sternal dehiscence requiring reoperation, mediastinitis, pneumonia and septicemia during the hospitalization.

Statistical Analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or mean (range), and categorical data were expressed as frequencies and percentages. Baseline characteristics were compared using analysis of variance (ANOVA), Kruskal-Wallis test or Chi-Square test, depending on their distribution and comparisons between groups were by Bonferroni method. Multivariate stepwise logistic regression models were used to identify predictive factors for prognosis. The prognosis variables that are continuous were categorized from their median for logistic regression. The independent variables that were entered into the models were BMI group, WBC_{pre} and changes in WBC (ΔWBC), age, gender, presence of diabetes, hypertension, cerebrovascular accident, chronic obstructive pulmonary disease and cancer. To convert the continuous variables, WBC_{pre} and ΔWBC, to binomial variable, we also divided the patients into two groups based on the median numbers of these two variables (7,300 for WBC_{pre} and 5,100 for ΔWBC). Data were analyzed using SAS 9.0 (SAS Institute Inc., Cary, NC, USA) and a P value < 0.05 was considered statistically significant.

Results

Eleven hundred and seventy-one patients were included in the final analysis. They were categorized prospectively into three groups based on their BMI: non-obese (BMI < 30 kg/m^2, n = 770), class I obese (BMI 30-34.9 kg/m^2, n = 247), and severely ($\geq$ class II) obese (BMI $\geq$ 35 kg/m^2, n = 154). The BMI criteria for obesity were based on the definition from the World Health Organization.

The demographic and clinical data of these patients are presented in Table 1. Severely obese patients tend to be younger than the other groups. The prevalence of diabetes and hypertension were higher in the obese and severely obese patients

Table 1. Demographic data and clinical characteristics of the patients.

Variables	Non-obese (n = 770)	Obese (n = 247)	Severely Obese (n = 154)	*P* value
BMI (kg/m^2)	25.2 ± 3.1	32.2 ± 1.4	40.0 ± 5.6	<0.01
Age (years)	63 ± 14	63 ± 12	60 ± 12*	0.01
Male	476(61.8)	141(57.1)	80(52.0)	0.05
DM	173(22.5)	95(38.5)	68 (44.2)	<0.01
HTN	451(58.6)	181(73.3)	121(78.6)	<0.01
CVA	32(4.2)	15(6.1)	6(3.9)	0.41
COPD	47(6.1)	17(6.9)	9(5.8)	0.87
Cancer	43(5.6)	16(6.5)	13(8.4)	0.37
Types of surgery				
CABG	389(50.5)	164(66.4)	94(61.0)	<0.01
CABG+VHD	87(11.3)	25(10.1)	10(6.5)	0.2
VHD	248(32.2)	49(19.8)	40(26.0)	<0.01
CHD	31(4.0)	3(1.2)	3(2.0)	0.06
Others	15(2.0)	6(2.4)	7(4.6)	0.15

Data are mean ± standard deviation or number of patients (%). DM: diabetes mellitus; HTN: hypertension; CVA: cerebral vascular accident; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass graft; VHD: valvular heart surgery; CHD: congenital heart disease; * P < 0.05 *vs.* non-obese.

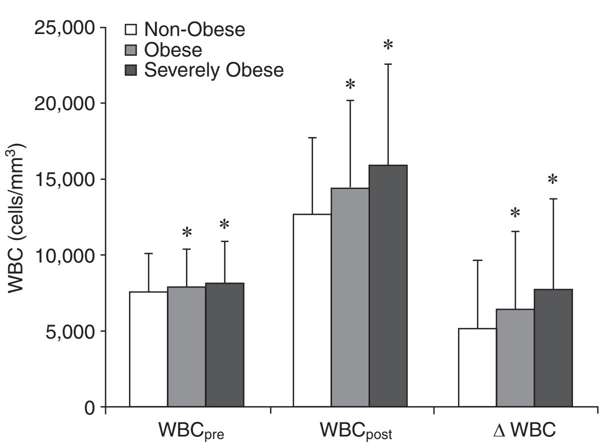

Fig. 1. Preoperative leukocyte count (WBC$_{pre}$), leukocyte count within 24 h of operation (WBC$_{post}$) and changes in WBC from the preoperative baseline to 24 h within the operation (ΔWBC) in non-obese, obese and severely obese patients. *P < 0.01 *vs.* the non-obese group.

than non-obese patients. Obese and severely obese patients had significantly higher WBC$_{pre}$ and WBC counts within 24 h after surgery (WBC$_{post}$). Changes in WBC (WBC$_{post}$ - WBC$_{pre}$) were also greater in obese and severely obese patients than non-obese patients (Fig. 1).

Table 2 shows the outcome measures in our study patients stratified by their BMI. The postoperative LOS was significantly longer in the severely obese patients than the other two groups. The length of ICU stay was also significantly longer in the severely obese patients than non-obese patients. Both obese and severely obese patients had significantly higher postoperative infection rates than non-obese patients. There were no differences among the groups in mechanical ventilation day, postoperative bleeding rate, ICU readmission rate within 14 days, reintubation rate or the survival rate.

Table 3 shows the significant predictors for clinical outcomes identified by the multivariate stepwise logistic regression models adjusted for age, sex and comorbidities. The ΔWBC is the only independent predictor of postoperative hospital LOS besides BMI. For every 1000/mm^3 increase in WBC from the baseline, there was an increase of 3% in the risk for longer postoperative hospital LOS in severely obese patients compared with non-obese and obese patients. For postoperative ICU stay and postoperative infection rate, both BMI and WBC$_{pre}$ are significant independent predictors.

Discussion

In our study, severely obese patients undergoing cardiac surgery had longer ICU stay and postop-

Table 2. Effects of obesity on clinical outcome parameters.

Variables	Non-obese (n = 770)	Obese (n = 247)	Severely obese (n = 154)	*P* value
Postoperative LOS (days)	9.1(3-91)	9.0(1-108)	10.1(4-151)*, ¶	0.03
ICU stay (days)	3.4(1-80)	3.4(1-50)	4.0(1-65)*	0.02
MV day (days)	1.8(0-64)	1.8(0-33)	2.7(1-127)	0.11
Postoperative infection	40(5.2)	24(9.7)*	19(12.3)*	<0.01
Postoperative bleeding	25(3.3)	4(1.6)	6(3.9)	0.31
Readmission to ICU < 14 days	59(7.7)	16(6.5)	16(10.4)	0.35
Reintubation	31(4.0)	10(4.1)	9(5.8)	0.54
Survival	758(98.4)	245(99.2)	152(98.7)	0.75

Data are presented as number of patients (%) or mean (range). LOS: length of stay; MV: mechanical ventilation. * Significantly different from the non-obese group; ¶ Significantly different from the obese group.

Table 3. Significant predictors for clinical outcomes identified by the multivariate stepwise logistic regression model.

	OR	95% CI	*P* value
	Postoperative length of hospital stay		
ΔWBC	1.35	1.07-1.71	0.01
	Length of ICU stay		
Severely obese	1.55	1.09-2.21	0.01
WBC_{pre}	1.28	1.01-1.63	0.04
	Postoperative infection		
Obese	1.78	1.05-3.04	0.03
Severely obese	2.31	1.29-4.13	<0.01
WBC_{pre}	2.25	1.39-3.65	<0.01

WBC_{pre}: preoperative WBC counts; ΔWBC: changes in WBC from the preoperative baseline to 24 h within the operation; OR: odds ratio; CI: confidence interval.

erative hospital LOS; and both obese and severely obese patients had increased postoperative infection rate. The increased chronic inflammatory status in these patients as represented by higher preoperative WBC counts and enhanced inflammatory response to surgical stress as shown by the greater rise in WBC counts in the postoperative period may further increase the risks for adverse postoperative outcomes.

Obesity is frequently cited as a risk factor for adverse outcomes of major operations such as cardiac surgery. In a case-control study, Prasad *et al*. compared the postoperative complications between obese and non-obese patient undergoing coronary artery bypass surgery (CABG). They found that obesity is an independent risk factor for perioperative morbidity, including respiratory difficulty, myocardial infarction, arrhythmia, and sternal dehiscence (19). Birkmeyer *et al*. examined 11,101 consecutive patients undergoing CABG. They found an association between BMI and sternal wound infection, but rates of postoperative bleeding were significantly lower in the obese and severely obese patients (1). Kuduvalli *et al*. examined 4,713 consecutive patients undergoing CABG. They found that severely obese patients were more likely to develop sternal wound infection, harvest site infection and have prolonged mechanical ventilation and postoperative stay (11). Our study included patients undergoing all open cardiac surgery and confirmed the increased postoperative complications, especially in severely obese patients. We did not observe longer duration of mechanical ventilation in our patient population, however, probably because these patients tended to have no baseline parenchymal lung diseases and the average total postoperative ventilator day was short (only 1 day).

The mechanisms by which obesity increased postoperative complications are complex. Chronic inflammation associated with obesity may be an important factor (4, 5). The adipose tissue can produce several proinflammatory cytokines, including IL-6, IL-12, IL-18, TNF-α, and WBC counts (2, 13). Compared to non-obese patients, the adipose tissue of obese patients contains more macrophages (23), which are a major producer of cytokines. Dixon *et al*. analyzed WBC counts of 477 normal subjects and found that subjects with higher BMI also have higher WBC counts. As the BMI decreases, so do the WBC counts (6). Herishanu *et al*. studied 327 patients with unexplained leukocytosis. Of these patients, 15.3% were obese. In a cohort of 3,716 non-smokers, subjects with leukocytosis had higher BMI and waist circumference (9). Our study also showed that obese and severely obese patients had higher preoperative WBC counts (Fig. 1). We further showed that, within 24 h after cardiac surgery, obese patients also had higher rise in WBC counts. Increases in WBC from the baseline to the immediate postoperative period were the greatest in severely obese patients. Thus, we deduce that obese patients likely have chronic low-grade inflammation and enhanced inflammatory response to stresses such as cardiac surgery. The state of chronic inflammation and the acute inflammatory response to surgical stress increased the risk for some surgical outcomes measures associated with obesity, including postoperative length of stay, ICU length of stay and postoperative infection rate. Therefore, a patient who is severely obese (BMI $\geq$ 35 kg/m^2) and has a preoperative WBC count of greater than 7,300 would have an 83% increase in the risk for longer ICU stay and a 256% increase in the risk for postoperative infection.

Although various reports demonstrate an association between obesity and postoperative complication as previously stated, several studies, however, have conversely supported an inverse relationship between BMI and postoperative morbidity and mortality (8, 12, 14, 17, 20, 21). This phenomenon is known as the 'obesity paradox'. Mullen *et al*. examined 118,707 patients undergoing nonbariatric general surgery (17). They found a reverse J-shaped relationship between the patient's BMI and risk of perioperative death. The risk of death was highest in the underweight and morbidly obese patients and lowest in the overweight and moderately obese patients. Mariscalco *et al*. conducted a meta-analysis to explore the obesity paradox observed in cardiac surgery (14). A total of 958,947 patients were included in their study. They found that there was an U-shaped association between mortality and BMI with lower mortality in overweight and obese class I and II patients, and increased mortality in underweight individuals. Hutagalung *et al*. examined 9,935 patients who were admitted to the surgical ICU (10). They found the overall incidence of organ failure during the ICU stay and the ICU mortality rate were similar among the obese and non-obese patients. They also found that being overweight or obese was independently associated with lower risk of 60-day in-hospital death.

One of the explanations for the obesity paradox is that the BMI is not a measure of body fat distribution. It does not discriminate between fat mass and lean mass. Oreopoulos *et al*. directly measured body composition using dual energy x-ray absorptiometry in 140 patients with systolic and/or diastolic heart failure and found that BMI misclassified body fat status in 41% patients (18). When directly measuring body composition, they found a significant association between increasing body fat and higher serum CRP levels, whereas increasing lean mass was associated with lower N-terminal pro-B-type natriuretic peptide levels. This finding demonstrates that overweight and mildly obese patients might not have more fat, but rather more preserved lean body mass, which would instead offer a survival benefit in these patients.

In our study, the postoperative LOS and the ICU stay were significantly longer in severely obese patients compared to non-obese patients. This phenomenon was not observed in obese patients, however. The ΔWBC were greatest in severely obese patients; it was also the only independent predictor of postoperative LOS in the severely obese patients. These findings might represent higher body fat composition rather than lean body mass in most of the severely obese patients, thus leading to a stronger inflammatory response after surgery. As stated previously, the obesity paradox should be interpreted with caution.

There are several limitations in this study. First, there may be many pre-existing inflammatory diseases, such as autoimmune disorders, which can alter the patients' leukocyte counts and inflammatory responses to the surgery. However, their disease activities may not be accurately reflected in medical records retrospectively. Patients with pre-existing inflammatory diseases were not excluded in this study. Additionally, we postulated that severely obese patients might have higher body fat composition that leads to more active inflammatory processes post-operatively. However, in this retrospective study, we were also unable to directly measure the patients' body fat composition. The results of the study highlight the need for future research to test the validity of our theory.

Conclusions

In conclusion, we showed that, in addition to BMI, preoperative WBC count and the increase in WBC from the baseline in the immediate postoperative period in patients undergoing cardiac surgery are independent predictors for postoperative adverse outcomes. Incorporating WBC data to BMI level may allow us to better stratify obese patients who are planning open heart surgery.

Conflict of Interests

The authors declare that there are no conflicts of interests. The authors declared that this study did not receive any grant.

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