Clinical Research

Higher Gensini Angiographic Score Predicts Poor Outcomes in High Weight Patients Undergoing Coronary Artery Bypass Grafting

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ABSTRACT

Objective: It is claimed in obesity paradox that high weight patients are protected from risks developed after coronary artery bypass grafting. However, the severity of coronary artery disease has not been clarified by using objective methods in the reports of obesity paradox. We believe that they have reached such a paradoxical finding as a result of operations in obese patients with relatively less risky coronary artery disease. Our purpose is to clarify whether angiographic severity (using Gensini score) affects early outcomes after coronary artery bypass grafting in high weight patients undergoing coronary artery bypass surgery.

Material and Method: Clinical and angiographic data from a total of 126 patients with a body mass index of ≥ 30 kg/m^2 undergoing isolated coronary artery bypass grafting were included. Primary outcome of interest was postoperative occurrence of early low cardiac output syndrome. Angiographic score of each patient was calculated according to the method described by Gensini. Factors associated with primary outcome were evaluated using multivariate analysis.

Results: Low cardiac output syndrome occurred in 27 patients (21.4%). In multivariate analysis cross clamp time (OR: 1.064, 95% CI 1.026-1.103, p:0.001), age (OR: 1.099, 95% CI 1.028-1.175, p:0.006) and Gensini score (OR: 1.025, 95% CI 1.006-1.044, p:0.008) were found to be independent predictors of low cardiac output syndrome after coronary artery bypass grafting.

Conclusion: Overweight patients with higher Gensini angiographic scores more tend to have low cardiac output syndrome after CABG than those with lower scores. Protective effects of obesity against postoperative risks after coronary artery bypass grafting should be revisited.

Keywords: *Coronary Artery Bypass Grafting, Coronary Artery Disease, Obesity, Low Cardiac Output Syndrome.*

ÖZET

Koroner Arter Bypass Greftleme Operasyonu Yapılan Fazla Kilolu Hastalarda, Operasyon Sonrası Kötü Sonuçların Yüksek Gensini Anjiografik Skor ile Tahmin Edilmesi

Amaç: Son zamanlarda literatürde obezite paradoksu konusu altında fazla kilolu hastaların koroner arter bypass cerrahisi sonrası, gelişen risklere karşı korunduğu ileri sürülmektedir. Ancak bu raporlarda koroner arter hastalığının ciddiyetinin objektif olarak tespit edilmediği ve nispeten daha az riskli koroner arter hastalığı bulunan obez bireylerdeki operasyonlar sonucunda böyle bir paradoks bulguya vardıkları inancındayız. Biz, koroner arter bypass cerrahisi geçiren fazla kilolu hastalarda, cerrahi sonrası erken dönem sonuçların anjiografik ciddiyet seviyesi (Gensini skorlama sistemi) ile belirtilmesini amaçladık.

Gereç ve Yöntem: Yalnızca koroner arter bypass greftleme operasyonu geçiren, vücut kitle indeksi ≥ 30 kg/m^2 (ortalama yaş 61.05±8.8 yıl, erkek/kadın oranı: 92/34) olan toplam 126 hastanın anjiografik ve klinik verileri çalışmaya dahil edildi. Primer olarak araştırılan postoperatif sonuç, erken dönem düşük kardiyak debi ve bununla ilişkili olan faktörlerdi. Her hastanın angiografik skorlaması, Gensini tarafından tanımlanan skor sitemine göre yapıldı. Primer sonuç ile ilişkili faktörler multivaryant analiz ile değerlendirildi.

Bulgular: Vücut kitle indeksi seviyeleri, 92 hastada 30-35 kg/m^2, 25 hastada 35-40 kg/m^2 ve 9 hastada 40 kg/m^2'nin üzerinde idi. 27 hastada düşük kardiyak debi görüldü. Multivaryant analizde, kross klemp süresi (OR: 1.064, %95 CI 1.026-1.103, p:0.001), yaş (OR: 1.099, %95 CI 1.028-1.175, p :0.006) ve Gensini skoru (OR: 1.025, %95 CI 1.006-1.044, p :0.008) koroner arter bypass greftleme sonrası düşük kardiyak debi gelişiminde bağımsız prediktör faktörler olarak bulundu.

Sonuç: Koroner arter bypass greftleme cerrahisi sonrasında, yüksek Gensini anjiografik skorlu fazla kilolu hastalar, düşük skorlu hastalara nazaran düşük kardiyak debi gelişimine daha eğilimlidirler. Koroner arter bypass greftleme operasyonu sonrası, gelişebilecek risklere karşı obezitenin koruyucu etkileri tekrar gözden geçirilmelidir.

Anahtar Sözcükler: *Koroner Arter Bypass Greftleme, Koroner Arter Hastalığı, Obezite, Düşük Kardiyak Debi Sendromu.*

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Obesity has become major global health problem in last three decades since its prevalence showed a substantial increase not only in developed world but also in developing counties (1). Obesity has important cardiovascular consequences that mainly arise from the adverse effects it produced in cardiac hemodynamics, structure and myocardial function (2). Supporting this, as it has been well established, obese or overweight people more tend to develop commonly observed cardiovascular diseases such as hypertension, heart failure and coronary artery disease (3).

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Nevertheless, there has been a growing body of evidence suggesting a paradoxical relationship between obesity and survival in patients with cardiovascular disease, which has been so called 'obesity paradox' and defined as overweight and obese patients have better survival from cardiovascular diseases than those with normal weight. Although it is arguable that a high body-mass index is a well-surrogate of obesity, as it falls short distinguishing between high lean body mass and fat body mass (4), obesity paradox in coronary heart disease has been well established depending not only on body-mass index evaluation but also on body fat or central obesity (5).

Obesity paradox has also gained popularity in the area of cardiac surgery. Several reports indicated the presence or absence of the paradox in patients undergoing coronary artery bypass grafting (CABG) (6-9). Presence of obesity paradox in CAPB patients, which has been suggested as lower early mortality, shorter hospital stay after surgery and lower rates of complications, may partly be attributed to the fact that these patients are being referred to surgery at an earlier age despite carrying a higher risk profile. Also, besides complex metabolic and biologic features that potentially play important role in disease pathogenesis, cardiovascular mortality in obese patients was demonstrated to be influenced also by cardiorespiratory fitness (10), which was also shown to affect morbidity and mortality after CABG (11).

A number of diseased vessels were almost always taken into account as a potential risk factor in obese patients undergoing CABG, considering that extensive coronary artery involvement in an earlier age is likely to be a natural consequence of the metabolic derangement seen in obesity. However, the relationship is yet to be established since various studies showed conflicting results. Some authors showed that presence of triple vessel disease was significantly less common in higher vs lower body weight patients (6, 7), whereas the opposite was also shown (8). It was also suggested that there was no significant difference among patients with normal vs overweight in regard to number of vessels involved (9) or the relationship was totally ignored by some others (12). Thus, whether extent of the coronary artery disease is truly associated with poor outcomes after CAGB has not yet been elucidated. We concluded a study on overweight patients undergoing isolated CABG, taking Gensini angiographic scores into account rather than number of vessels involved in order to better quantify the effect of disease extension on poor outcomes after surgery.

MATERIAL AND METHOD

This was a retrospective observational cohort study and made up of patients undergoing isolated CABG in tertiary care hospital between February 2014 and April 2015. Search of the hospital registry database revealed that a total of 436 patients underwent isolated CABG between the dates given. Among these, a total 152 patients aged between 30 to 75 years and having a BMI more than 30 kg/m^2 were included into the initial assessment. Patients undergoing reoperation (2 patients) or emergency operation (7 patients) and those with a low ejection fraction (30 %, 8 patients) or those having multiple comorbidities including severe chronic obstructive pulmonary disease (3 patients), low platelet count (30.000, 2 patients) and advanced stage renal failure (glomerular filtration rate 25, 4 patients) were excluded from the study (n =26). Final analysis included a total 126 patients (mean age 61.05±8.80 years, ranged from 37 to 73 years, male: female ratio = 92:34). None of patients had neurological motor deficit. A clear indication for heart valve or aortic surgery was not present in anyone of patients.

Patient demographics, counselling charts and laboratory results were recorded to reveal baseline characteristics of patients. Body-mass index values were based on measurements performed during spirometry assessment which is routinely being performed within a couple of days before the operation. Angiography views of the patients were obtained from the angiography database of the hospital and assessed by an independent cardiologist blinded to the outcome. Angiographic score of each patient was calculated according to the method described by Gensini (13).

Primary outcome of interest was postoperative occurrence and persistence (at least 4 hours) of early cardiac output syndrome which was defined as persistent hypotension, central venous pressure increase, low urine output and/or altered mental status. Secondary outcomes of interest were surgery related mortality and potential complications including, early myocardial infarction (a troponin level of ≥20 ng/ml in presence of hemodynamic derangement), sternal wound infection, drainage, respiratory distress, acute renal failure (sharp increase in creatinine level above 2.0 mg/dl), arrhythmia, prolonged intensive and hospital stay.

Sample size estimation:

A priori estimation was performed to find out the minimum sample size required to establish the relationship between higher angiographic scores and poor outcomes after CABG. We could not any study providing significant differences in mean Gensini scores between patients having or not having the outcome measure. However, in a recent study, Sinning et al (14) reported a cut-off value of 75.5 for Gensini score to predict worse outcomes including cardiovascular death and related outcomes. Therefore, we assumed that a ± 10% deviation from this cut-off value (67.95 vs. 83.05, with a standard deviation of 25.0 in each group) would probably produce clinically relevant outcomes (i.e. difference in Gensini scores between patients having or not having LCOS after CABG). Using the G-Power Statistical Software, setting a significance level of α:0.05 and power level of β:0.20, we found that a minimum of 118 patients were required for the present study. Search

of the database was continued until slightly exceeding this level.

Statistical analysis:

Statistical analyses were performed using SPSS (Statistical Package for the Social Science) software. Continuous data following a normal distribution were expressed as mean and standard deviation, while those not following a normal distribution were expressed as median and ranges. Besides, categorical variables were reported as frequency and percentage. Independent sample T test for continuous data with a normal distribution, Mann Whitney U test for continuous data with non-normal distribution, Pearson Chi-Square test for categorical variables were performed for the group comparisons. In the analysis of predictive risk factor for adverse outcome, univariate predictors were determined with the univariate logistic regression analysis and an odds ratio was calculated for each parameter. Variables having a p value < 0.01 in the univariate analysis and non-correlated each other were included into the multivariate logistic regression analysis. Appropriateness of the model was tested using Akaike information criterion. P value ≤0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics and operative data were given in table 1. Body-mass index levels were ranging between 30 and 35 kg/m^2 in 92 patients (73.0%), 35 and 40 kg/m^2 in 25 patients (19.8%) and more than 40 kg/m^2 in 9 patients (7.1%).

Table 1. *Baseline characteristics and operative data.*

Variables	n (%) / mean±SD / median (min-max)
Age (year)	61.1±10.4
Male gender	92 (73.0)
BMI (kg/m^2)	33 (30-46)
30-35 kg/m^2	92 (73.0)
35-40 kg/m^2	25 (19.8)
> 40 kg/m^2	9 (7.1)
EF (%)	55 (22-65)
Hypertension	71 (56.3)
Diabetes	48 (38.1)
Hyperlipidemia	30 (23.8)
COPD	22 (17.5)
Unstable angina	44 (34.9)
Gensini score	51 (8-163)
Beta receptor antagonist	40 (31.7)
ACE inhibitors	34 (27.0)
Statins	25 (19.8)
Hypothyroidism	11 (8.7)
Off-Pump Surgery	12 (9.5)
Cross clamp time (min)	54 (16-194)
CPB time (min)	95 (31-412)
Retrograde cardioplegia	48 (38.1)
Complete revascularization	110 (85.9)

ACE: Angiotensin converting enzyme, BMI: body mass index, CPB: Cardio pulmonary bypass COPD: chronic obstructive pulmonary disease, EF: ejection fraction. Gensini score: Angiographic score developed by Gensini.

Table 2 shows postoperative outcomes. Low cardiac output syndrome occurred in 27 patients (21.4%). Among these, elevated lactate concentration (>2 mmol/L), elevated CVP (>10 cmH_2O), oliguria (<10 ml/h urine output) and dopamine infusion (3-5 µg/kg/min) were present in these patients whereas hypotension was present in 22 patients, altered mental status in 12 patients, catecholamine infusion in 16 patients. Placement of IABP was performed to 25 patients and counter-pulsation was continued for at least 2 days.

Table 2. *Postoperative outcomes.*

Variables n (%) / mean±SD / median (min-max)	LCOS (+) (n : 27)	LCOS (-) (n :99)	All Patients (n : 126)	*p*
Mortality	7 (25.9)	0	7 (5.6)	<0.001*
Postoperative MI	6 (22.2)	5 (5.1)	11 (8.7)	0.01*
Sternal wound infection	2 (7.4)	2 (2.0)	4 (3.2)	0.20
Total amount of drainage (ml)	529±305	541±185	538±222	0.89
Respiratory distress	8 (29.6)	9 (9.1)	17 (13.5)	0.01*
Atrial fibrillation	9 (33.3)	3 (3.0)	12 (9.5)	<0.001*
Acute renal failure	9 (33.3)	9 (9.1)	18 (14.3)	0.003*
LOS of ICU (day)[a]	2 (1-12)	1 (1-6)	1 (1-12)	<0.001*
LOS of Hospital (day)[a]	9 (6-28)	7 (5-48)	7 (5-48)	0.04*

ICU: Intensive care unit, LOS: length of stay, MI: myocardial infarction, SD: standard deviation.
[a]: Included only patients survived after the operation (n :119).
**: Statistically significant parameter.*

Overall mortality occurred in 7 patients, all of whom died due to LCOS; 2 patients died of early reperfusion injury and resultant hemodynamic derangement within 12 hours after the operation. In the remaining 5 patients death occurred within a range of 6 to 18 days and was due to various causes including; respiratory distress syndrome and ventilator associated pneumonia (3 patients), acute renal failure (1 patient), sepsis and multiorgan failure (1 patient). Overall, postoperative morbidities including respiratory distress, atrial fibrillation, acute renal failure (i.e. need for hemodialysis) and prolonged ICU stay were significantly more common in patients with LCOS than those without LCOS after CABG.

Parameters with a p value of less than 0.10 in univariate analysis were put into multivariate analysis (Table 3), except for retrograde cardioplegia was not included since it was found significantly correlated with both Gensini scores and cross clamp times. No other significant correlation was found among study parameters. In multivariate analysis, cross clamp time (OR: 1.064, 95% CI 1.026-1.103, p =0.001), age (OR: 1.099, 95% CI 1.028-1.175, p =0.006) and Gensini score (OR: 1.025, 95% CI 1.006-1.044, p =0.008) were found to be independent predictors of LCOS after CABG (Table 4).

Table 3. *Univariate analysis for the development of LCOS after CABG.*

Variables	OR	95%CI lower	95%CI upper	*p*
Age (year)	1.06	1.02	1.11	0.009*
Male gender	1.07	0.41	2.82	0.89
BMI (kg/m^2	0.95	0.83	1.09	0.50
EF (%)	0.94	0.90	0.98	0.002*
Hypertension	1.42	0.59	3.40	0.44
Diabetes	0.94	0.39	2.28	0.90
Hyperlipidemia	1.16	0.43	3.08	0.77
COPD	1.96	0.71	5.44	0.20
Unstable angina	1.38	0.57	3.30	0.48
Gensini score	1.02	1.01	1.03	0.003*
Beta receptor antagonist	0.70	0.27	1.82	0.47
ACE inhibitors	2.27	0.93	5.58	0.07*
Statins	0.90	0.30	2.67	0.85
Hypothyroidism	1.42	0.35	5.77	0.62
Off-pump surgery	0.31	0.04	2.50	0.27
Cross clamp time (min)	1.06	1.02	1.09	0.001*
Retrograde cardioplegia	4.35	1.70	11.16	0.002*
Complete revascularization	2.06	0.44	9.67	0.36

ACE: Angiotensin converting enzyme, BMI: body mass index, CABG: coronary artery bypass grafting, CI: Confidence interval, COPD: chronic obstructive pulmonary disease, EF: ejection fraction, LCOS: low cardiac output syndrome, OR: Odds ratio.
Gensini score: Angiographic score developed by Gensini.
**: Variables having a p value < 0.10 in the univariate analysis.*

Table 4. *Multivariate analysis for the development of LCOS after CABG.*

Variables	OR	95%CI lower	95%CI upper	*p*
Cross clamp time (min)	1.06	1.03	1.10	0.001
Age (year)	1.10	1.03	1.18	0.006
Gensini score	1.03	1.01	1.04	0.008

CABG: Coronary artery bypass grafting, CI: Confidence interval, LCOS: low cardiac output syndrome, OR: Odds ratio, Gensini score: Angiographic score developed by Gensini.

DISCUSSION

To our knowledge, the present study was the first investigating the relationship between angiographic severity and early postoperative hemodynamic derangement in overweight patients. We found that Gensini angiographic severity score was also an independent predictor of LCOS after CABG, together with those already known including cross clamp time and age.

In line with a number of previous studies, postoperative mortality and morbidities were not too more common in this study but were close to mild risky population, roughly suggesting that obesity itself does not add too much risk for development of various complications after CABG. However, the number of our patients was limited to prove or disprove the presence of an obesity paradox since this term has been suggested upon researching on thousands of patients. Nevertheless, among the whole of overweight patients, some are supposed to be more likely to develop LCOS after surgery, which is often the case in all different populations undergoing CABG. Our retrospective observations provided that having higher angiographic severity scores might be the unique characteristics of such patients.

Why investigate whether there is a relationship between angiographic severity and CABG outcomes, whilst obesity paradox and its relevance have already been revealed in over weight population undergoing CABG? First, previous studies have fallen short in giving robust data establishing such paradox and been biased by several factors. In a recent study by Ardeshiri et al. (15), authors reported that there was no significant difference between patients with a BMI lower or higher than 30 kg/m^2 in regard to many CABG outcomes. However early outcomes such as cardiogenic shock, requirement of intra-aortic balloon pump and myocardial infarction occurred in only a few patients in overweight group where total number of patients was 60. In another study on overweight patients undergoing CABG, Benedetto et al. (16) reported that obesity was not protective for late date after CABG although overweight status was not associated with increased risk of death early after the operation. Although this study results were based on 3821 obese patients initially, a propensity score analysis was performed to match two groups by confounders. Final analyses were performed n matched 203 patients. This approach is subject to criticism since an overmatch bias seems likely because patients with known risk factors that are almost unique to obese individuals in real life have totally been left outside the analysis. Producing a near-normal except high-weight population, this study fell short focusing the main problematic proportion of the overweight patients undergoing CABG operation. Stamou et al. (17) reporterd the presence of obesity paradox in their study on 2440 patients undergoing CABG (isolated and combined) but, in controversy, they did not perform any baseline matching between patients with or without high BMI. Patients in high weight and obesity groups were significantly younger and they significantly more tend to have diabetes and three vessel diseases, this time producing and important patient selection bias. Le-Bert et al. (8) sought to clarify the same issue on elderly obese patients undergoing CABG and reported that obesity in elderly did not demonstrate an increased risk of postsurgical complications after CABG. In this study, intra-aortic balloon pump was required in 45 (26.9%) vs 27 (28.7%) patients in normal vs overweight patients, respectively (p :0.95). These figures, being close to those we found in our study, indicates that one-fourth of patients with high BMI have low cardiac output syndrome after CABG, if they are not young enough to tolerate harmful effects of cardiopulmonary bypass on myocardium.

Second, and more important, is that metabolic obesity rather than anatomic obesity has recently increased in popularity since metabolically healthy subjects with high BMI have a lower prevalence of cardiac risk factors, suggesting a new definition for obesity that should be based on fat distribution rather than body mass index (18). Recently there have been many studies pointing out the importance of distinguishing metabolically healthy obese patients from those with abnormal metabolic status. Mørkedal et al. (19) reported that obesity without metabolic abnormalities does not increase the risk of acute myocardial infarction but there was signi-

ficant increase in risk of heart failure. Supporting this, Hamer et al. (20) reported that metabolically healthy obese individuals were not at increased risk of cardiovascular disease. On the contrary, Chang et al. (21) reported that patients with metabolically healthy obesity had a higher prevalence of subclinical atherosclerosis, indicating that obesity is harmful to coronary arteries regardless of its association with metabolic derangement. Nevertheless, the opposite of these findings was defended Rhee et al. (22). Importance of metabolically healthy status in overweight patients has thus still been controversial especially when cardiovascular disease prevalence or death was taken into consideration as the outcome parameters. Kwon et al. (23) sought to clarify the relationship between metabolic obesity and angiographic coronary artery disease. Based on Korean national classification, they defined the metabolic obesity as presence of 3 or more of the following; larger waist circumference, elevated high-density lipoprotein cholesterol and triglyceride level, high blood pressure and diabetes. Their findings were interesting; metabolically obese but normal weight individuals had higher severity in angiography than metabolically healthy normal weight individuals after adjustment for various risk factors and metabolically obese individuals had higher angiographic severity than non-metabolically obesity after adjustment for age and sex. This study particularly draws attention to the importance of distinguishing patients with more severe coronary artery disease extension from those having mild involvement of coronary arteries with atherosclerosis.

We think that our study provided some information regarding the identification of more risky ones among those patients with high BMI submitted to CABG. Since the correlation between angiographic severity and presence of some cardiovascular risk factors (co-existence has recently been called as metabolic obesity) has been well established (24), it is not surprising to find out that angiographic severity may play an important role as an independent risk factor for development of LCOS after CABG.

Our study had several limitations. Retrospective design and lack of control group comprised of normal weight individuals was the major limitation. Use of certain criteria for determination of metabolic obesity and giving more detailed information which proportion our patients were indeed metabolically obese would have add much more information to the study. Finally, long term data could not to be provided because more than >50% patients could not respond to our invitation and also due to lack of adequate registry data regarding coronary artery disease outcomes.

In conclusion, we found that overweight patients with higher Gensini angiographic scores more tend to have low cardiac output syndrome after CABG than those with lower scores. Therefore, obesity paradox or in other words, protective effect of being overweight against adverse outcomes after CABG should be revisited in further study focusing on angiographic severity and its association with metabolic obesity since there seems to be an important cause and effect relationship between these two parameters.

Conflict of interest: None declared.

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