Predictors of Low Cardiac Output Syndrome After Isolated Coronary Artery Bypass Grafting

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SUMMARY

Low cardiac output syndrome (LCOS) is one of the most important complications following coronary artery bypass grafting (CABG) and results in higher morbidity and mortality. However, few reports have focused on the predictors of LCOS following CABG. This study aimed to evaluate the predictors of LCOS following isolated CABG through the review of 1524 consecutive well-documented patients in a single center, retrospective trial.

The relevant preoperative and intraoperative data of patients with complete information from medical records undergoing isolated CABG from January 2010 to December 2013 in our center were investigated and retrospectively analyzed. LCOS was considered when the following criteria were met: signs of impairment of body perfusion and need for inotropic support with vasoactive drugs or mechanical circulatory support with an intra-aortic balloon pump to maintain systolic blood pressure greater than 90 mmHg.

LCOS developed in 205 patients following CABG, accounting for 13.5% of the total population. The in-hospital mortality in the LCOS group was significantly higher than that in the non-LCOS group (25.4% versus 1.8%, $P < 0.0001$). In addition to the length of ICU stay and postoperative hospital stay, LCOS was correlated with negative cerebral, respiratory and renal outcomes. Through univariate analysis and then logistic regression analysis, the predictors of LCOS following CABG included older age (age > 65 years) (OR = 1.85, 95%CI 1.27-3.76), impaired left ventricular function (OR = 2.05, 95%CI 1.53-4.54), on-pump CABG (OR = 2.16, 95%CI 1.53-4.86), emergent CPB (OR = 9.15, 95%CI 3.84-16.49), and incomplete revascularization (OR = 2.62, 95%CI 1.79-5.15).

LCOS following isolated CABG caused higher mortality, higher rates of morbidity, and longer ICU and postoperative hospital stays. Older age, impaired left ventricular function, on-pump CABG, emergent CPB, and incomplete revascularization were identified as 5 predictors of LCOS following isolated CABG surgery. (Int Heart J 2015; 56: 144-149)

Key words: Low cardiac output, Coronary artery bypass grafting, Predictor

Low cardiac output syndrome (LCOS) is one of the most important complications following coronary artery bypass grafting (CABG). LCOS following CABG causes higher mortality, and higher rates of morbidity in the forms of pulmonary complications, myocardial infarction, stroke, renal failure, and need for reoperation.¹⁻⁵ In addition, patients who develop LCOS have prolonged ventilatory support and longer duration of intensive care unit (ICU) and hospital stays, which are also reported as risk factors associated with higher mortality.^{6,7} Higher morbidity and prolonged ventilatory support coincide with longer ICU and hospital stays, which might contribute to increase the economic impact of this entity. Obviously, it becomes crucial for clinicians to identify the predictors of LCOS following CABG surgery in order to optimize perioperative risk factors involved in strategies to reduce the incidence of LCOS following CABG.

Previous studies have reviewed the concept that LCOS

following cardiac surgery resulted from a combination of risk factors, partly due to the nature of the patient population and partly to the process of patient care.⁷⁻⁹ However, few reports have focused on the independent risk factors for LCOS following CABG surgery.^{10,11} This study sought to evaluate the predictors of LCOS following CABG surgery by reviewing 1524 consecutive well-documented patients who underwent isolated CABG in our center from January 2010 to December 2013, in order to optimize perioperative risk factors involved in strategies to reduce the incidence of LCOS following CABG surgery.

METHODS

Definition of LCOS following CABG: LCOS was considered when the following criteria were met before discharge from

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the first hospitalization in the intensive care unit immediately after isolated CABG surgery^{11,12}: 1) Need for inotropic support with vasoactive drugs (dopamine 4 µg/kg/minute at least for a minimum of 12 hours and/or dobutamine and/or milrinone and/or epinephrine and/or noradrenaline) or mechanical circulatory support with an intra-aortic balloon pump to maintain systolic blood pressure greater than 90 mmHg after correction of all electrolytes and blood gas abnormalities while adjusting preload volume to its optimal values; 2) Signs of impairment of body perfusion (cold extremities, hypotension, oliguria or anuria, lowered level of consciousness, or a combination of these signs) after correction of all electrolytes and blood gas abnormalities while adjusting preload volume to its optimal values.

Subjects: After approval by the ethics committee, in accordance with the “Declaration of Helsinki”, we reviewed the records of consecutive well-documented patients undergoing isolated CABG in our center from January 2010 to December 2013. Any patient with incomplete information from medical records was excluded from the study. Data collection was performed by trained staff (two people) who were unaware of the purpose of the study.

The coronary anatomy of each patient, in association with the preoperative characteristics, was carefully evaluated for assignment to off-pump CABG or on-pump CABG. In every patient complete anatomic revascularization of all diseased vessels with a luminal diameter greater than or equal to 1 mm was considered necessary. If the operating surgeon judged a complete revascularization feasible on the beating heart, off-pump CABG was scheduled. In patients in whom the location or the quality of the target vessels and the preoperative characteristics (for example, large left ventricle) was considered to make off-pump revascularization technically too challenging, on-pump CABG was scheduled. All procedures (either off-pump or on-pump CABG) were performed by the same surgical team and there were no differences in the rate of adoption of off-pump CABG between the different surgeons. In our center, off-pump CABG had been performed routinely for > 5 years before the launch of the trial, and all of the operations were performed by 3 surgeons highly experienced in both off-pump and on-pump surgery (each of the 3 participating surgeons performed at least 50% of their CABG procedures as off-pump CABG).

Clinical data: The relevant preoperative and intraoperative data of all selected patients were investigated and retrospectively analyzed. Preoperative data included older age (age > 65 years), gender (male or female), obesity (body mass index > 30 kg/m²), smoking (reported by a patient; active or inactive for less than 10 years), hypertension (reported by a patient and/or use of antihypertensive medication), diabetes mellitus (reported by a patient and/or use of oral hypoglycemic medication and/or insulin), hyperlipidemia, chronic obstructive pulmonary disease (COPD) (dyspnea or chronic cough and prolonged use of bronchodilators or corticosteroids and/or compatible radiological changes - hypertransparency by hyperinflation and/or rectification of ribs and/or rectification diaphragmatic), renal dysfunction (creatinine more than 2.5 mg/dL or requiring dialysis), prior cerebrovascular accident, recent myocardial infarction (MI) (evidence of MI within the last 30 days before surgery), prior heart operation, left main trunk disease, SYNTAX score,¹³ impaired left ventricular function (left ventricular ejection fraction (LVEF) < 50%, measured by Dop-

pler ultrasound), and large left ventricle (left ventricular end-diastolic diameter (LVEDD) > 65 mm, measured by Doppler ultrasound). Intraoperative data included emergency surgery (during acute myocardial infarction, ischemia not responding to therapy with intravenous nitrates, cardiogenic shock), use of an internal mammary artery, use of a radial artery, low number of bypass conduits ($n < 3$), on-pump CABG or off-pump CABG, emergent cardiopulmonary bypass (CPB) (had to be switched from off-pump to on-pump CABG during surgery), use of an intra-aortic balloon pump (IABP), and completeness of revascularization (comparing significantly stenotic vessels at cardiac catheterization with surgically grafted coronary vessels; grafting of all the significantly stenotic coronary vessels was considered complete revascularization).

In addition, we also assessed the following clinical outcomes: postoperative incidence of respiratory failure (prolonged ventilator therapy > 72 hours, or re-intubation), stroke (new permanent neurological event; early stroke: within 24 hours and delayed stroke greater than 24 hours postoperatively), acute renal failure (ARF) (creatinine greater than 2.5 mg/dL for more than 7 days or requiring dialysis), and deep sternal wound infection (DSWI) (bone related; any drainage of purulent material from the sternotomy wound and instability of the sternum), length of ICU stay and hospital stay, and surgical mortality (death that occurred during the same hospitalization or within 30 days of operation).

Surgical procedure: OPCAB procedure was performed through a median sternotomy. Patients were heparinized with 1 mg/kg intravenously to achieve activated clotting time > 300 seconds. The central temperature, which was measured by a pulmonary artery catheter, was maintained above 36°C using a warm mattress, a forced warm air blanket, and a fluid warmer where necessary. The heart was displaced using a posterior pericardial stitch, large (12 × 70 cm) gauze swabs and a tissue stabilizer (Octopus, Medtronic Corporation, Minneapolis, MN). Body position changes and gravity support (Trendelenburg, right and left table rotations), in combination with the administration of vasoactive agents (for example, norepinephrine), were carried out to stabilize hemodynamics during OPCAB. A CO₂-blower/NaCl mister device was used in situations where a bloodless field was not achieved with proximal target vessel occlusion. An intracoronary shunt (Medtronic Corporation, Minneapolis, MN) was used during grafting. Blood loss was collected in a cell salvage device, and the salvaged blood was re-infused into the patient before the completion of surgery. The sequence of grafting was always from the left internal mammary artery to the left anterior descending coronary artery first, followed by grafting of the circumflex coronary artery and right coronary artery using a radial artery or saphenous vein. Before proximal anastomosis of grafts was performed, ascending aortic sclerosis or calcification was assessed based on the following parameters: preoperative imaging examination, including X-rays as well as echocardiography, and intraoperative palpation and transesophageal echocardiography. The “No-touch” aorta technique or eNclose (Novare Surgical Systems Inc., American) was available when moderate to severe sclerosis or calcification was detected. The quality of an anastomosis was assessed after grafting with the use of a transit-time flow probe (Medistim Butterfly Flow Meter, Oslo, Norway).

For those patients who underwent CCABG, CPB was in-

stituted with a single two-stage right atrial cannulation and an ascending aorta perfusion cannulation. Standard management included membrane oxygenators, arterial catheter filters, and non-pulsatile flow of 2.4 L/minute/m², with a mean arterial blood pressure greater than 50 mmHg. Patients were heparinized with 3 mg/kg to achieve an activated clotting time > 480 seconds. Heparin was neutralized with 1 mg protamine sulfate per 1 mg given. Moderate hemodilution (hematocrit, 20% to 25%) was used during CPB. The patients were routinely cooled to 32°C for grafting. The myocardium was protected using intermittent perfusion of cold blood cardioplegic solution at 4°C and in a ratio of 1:4. The cold blood cardioplegia was composed of sodium chloride at 132 mmol/L, potassium chloride at 16 mmol/L, calcium chloride at 1.8 mmol/L, magnesium sulphate at 15 mmol/L, procaine at 0.05 mmol/L, and sodium bicarbonate at 19 mmol/L. The cardioplegia solution was initially administered antegradely and retrogradely, and thereafter continuously retrogradely. All anastomoses were sutured by hand.

Statistical analysis: Statistical analysis was performed using the SPSS17.0 statistical software package. Univariate analysis, using the unpaired *t*-test to compare measurement data and Fisher's exact test to compare enumeration data, was performed to assess statistically significant variables, and those with *P* < 0.10 were then entered into a backward logistic regression analysis to identify the independent risk factors for LCOS following CABG surgery. The regression coefficients of factors with *P* < 0.05 were calculated. The "Hosmer-Lemeshow goodness of fit coefficient" was computed for the regression model. All *P* values < 0.05 were considered to be statistically significant.

RESULTS

Study population: From January 2010 to December 2013, 1746 consecutive patients suffering from coronary artery disease received isolated CABG in our center. A total of 222 patients were excluded from this study due to incomplete information from medical records, leaving 1524 well-documented patients (1186 males and 338 females, with a mean age of 63.2 ± 8.9 years) for data analysis. Coronary artery angiography prior to CABG surgery revealed double vessel disease in 244 patients (16.0%), triple vessel disease in 1279 patients (83.9%), and left main coronary artery disease in 473 patients (31.0%). The SYNTAX score was low (≤ 22) in 265 patients (17.3%), intermediate (23-32) in 714 patients (46.9%), and high (≥ 33) in 545 patients (35.8%). Selective CABG surgery was performed in 94.0% (*n* = 1433) of the patients while 72.5% (*n* = 1105) of the patients underwent CABG without CPB. The remaining patients (*n* = 419) underwent cardioplegic arrest CABG. The number of bypass conduits ranged from 1 to 5 (mean, 3.4 per patient). An internal mammary artery was used as a bypass conduit in 1420 (93.2%) patients, radial artery in 533 (35.0%) patients, and great saphenous vein graft in 1434 (94.1%) patients. After CABG surgery, 205 patients accounting for 13.5% of the total population developed LCOS, and 76 patients accounting for 5.0% of the total population died.

Univariate analysis: The results of the univariate analysis are shown in Table I. It can be observed that older age (age > 65 years), diabetes mellitus, preoperative renal dysfunction, recent

MI, impaired left ventricular function (LVEF < 50%), large left ventricle (LVEDD > 65 mm), emergency surgery, on-pump CABG, emergent CPB, and incompleteness of revascularization were relative risk factors for LCOS following CABG.

Multivariate analysis: Those variables with *P* < 0.10 obtained through the univariate analysis were then entered into a backward logistic regression analysis (LCOS or not as independent variable, variables with *P* < 0.10 obtained through univariate analysis as dependent variables). As shown in Table II, predictors of LCOS following isolated CABG included older age (age > 65 years) (OR = 1.85, 95% CI 1.27-3.76, *P* = 0.001), impaired left ventricular function (LVEF < 50%) (OR = 2.05, 95% CI 1.53-4.54, *P* = 0.005), on-pump CABG (OR = 2.16, 95% CI 1.53-4.86, *P* = 0.018), emergent CPB (OR = 9.15, 95% CI 3.84-16.49, *P* < 0.0001) and incomplete revascularization (OR = 2.62, 95% CI 1.79-5.15, *P* = 0.007). The Hosmer-Lemeshow goodness of fit coefficient of this model was 0.91.

Clinical outcomes: Patients who developed LCOS following CABG surgery showed higher rates of respiratory failure (38.1% versus 7.2%), stroke (32.2% versus 3.6%), ARF (22.4% versus 5.7%), DSWI (7.3% versus 1.6%), and surgical mortality (25.4% versus 1.8%) compared with those without this complication. In addition, patients who developed LCOS following CABG surgery had longer duration of ICU and postoperative hospital stays (7.3 ± 2.8 versus 2.1 ± 1.0 days, 21.3 ± 6.4 versus 8.4 ± 2.3 days) compared with those without this complication.

DISCUSSION

LCOS is one of the most important complications following CABG surgery. Other than the studies of Bianco and Sá on LCOS following CABG, few studies have been published.^{10,11} Bianco and colleagues evaluated 814 patients undergoing myocardial revascularization surgery between 2002 and 2003 in Sao Paulo, and reported that LCOS affected 16.1% of the total population.¹⁰ Sá and colleagues retrospectively evaluated 605 consecutive patients who underwent CABG surgery from May 2007 to December 2010 in Brazil, and found that the incidence of LCOS following CABG was 14.7%.¹¹ The incidence of LCOS following CABG surgery in this study was similar to other series mentioned above (13.5%).

LCOS causes higher morbidity and surgical mortality after CABG surgery. In this study, we also observed that patients who developed LCOS after CABG surgery showed significantly higher rates of morbidity in the forms of pulmonary complications (respiratory failure), stroke, renal failure, and deep sternal wound infection, and longer ICU stay as well as postoperative hospital stay than those patients without this complication. Some previous studies implicated LCOS as a risk factor for mortality.⁶ The Bianco and Sá studies identified very high mortality associated with LCOS following CABG (54.2% and 52.8%, respectively).^{10,11} It was observed that 25.4% of patients who developed LCOS following CABG surgery in our series died. The surgical mortality in those patients suffering from LCOS following CABG in our series was far below other series mentioned above. The reason for this difference can be the low rate of incomplete revascularization and high rate of off-pump CABG surgery (avoiding CPB and its negative effects) in our series. In addition, in a retrospective re-

Table I. Comparison of Preoperative and Intraoperative Data Between the Two Groups

Factors	LCOS (n = 205)	Non-LCOS (n = 1319)	P
Preoperation			
Older age (age > 65 years)	135 (65.9%)	484 (36.7%)	< 0.0001
Female	52 (25.4%)	286 (21.7%)	0.2408
Obesity (BMI > 30 kg/m ²)	93 (45.4%)	527 (40.0%)	0.1471
Smoking	108 (52.7%)	654 (49.6%)	0.4529
Hypertension	143 (69.8%)	844 (64.0%)	0.1162
Diabetes mellitus	126 (61.5%)	648 (49.1%)	0.0012
Hyperlipemia	72 (35.1%)	411 (31.2%)	0.2595
COPD	32 (15.6%)	192 (14.6%)	0.6724
Renal dysfunction	8 (3.9%)	16 (1.2%)	0.0100
Prior cerebro-vascular accident	52 (25.4%)	295 (22.4%)	0.3705
Recent MI	71 (34.6%)	305 (23.1%)	0.0006
Prior heart operation	3 (1.5%)	10 (0.8%)	0.4013
Impaired left ventricular function	101 (49.3%)	528 (40.0%)	0.0146
Large left ventricle	73 (35.6%)	347 (26.3%)	0.0071
Left main trunk disease	75 (36.6%)	398 (30.2%)	0.0740
Triple vessel disease	180 (97.6%)	1099 (81.8%)	0.1247
Double vessel disease	25 (2.4%)	219 (18.1%)	0.1244
SYNTAX score			
Low: ≤ 22	20 (9.8%)	245 (18.6%)	0.1824
Intermediate: 23-32	103 (50.2%)	611 (46.3%)	
High: ≥ 33	82 (40.0%)	463 (35.1%)	
Intra-operation			
Emergency surgery	17 (8.3%)	53 (4.0%)	0.0111
Use of IMA	186 (90.7%)	1234 (93.6%)	0.1374
Use of radial artery	76 (37.1%)	457 (34.6%)	0.5290
On-pump CABG	95 (46.3%)	324 (24.6%)	< 0.0001
Emergent CPB	7 (3.4%)	5 (0.3%)	0.0003
Use of IABP	8 (3.9%)	27 (2.0%)	0.1263
Number of bypass < 3	11 (5.4%)	46 (3.5%)	0.2314
Incomplete revascularization	29 (14.1%)	68 (5.2%)	< 0.0001

LCOS indicates low cardiac output syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; IMA, internal mammary artery; CPB, cardiopulmonary bypass; and IABP, intra-aortic balloon pump.

Table II. Multivariate Regression Results for Independent Risk Factors

Predictors	OR value	95%CI	P
Older age (age > 65 years)	1.85	1.27-3.76	0.001
Impaired left ventricular function	2.05	1.53-4.54	0.005
On-pump CABG	2.16	1.53-4.86	0.018
Emergent CPB	9.15	3.84-16.49	< 0.0001
Incomplete revascularization	2.62	1.79-5.15	0.007

CPB indicates cardiopulmonary bypass.

Table III. Clinical Outcomes Between the Two Groups

	LCOS (n = 205)	Non-LCOS (n = 1319)	P
Respiratory failure	78 (38.1%)	95 (7.2%)	< 0.0001
Stroke	66 (32.2%)	48 (3.6%)	< 0.0001
ARF	46 (22.4%)	75 (5.7%)	< 0.0001
DSWI	15 (7.3%)	21 (1.6%)	< 0.0001
ICU stay (days)	7.3 ± 2.8	2.1 ± 1.0	< 0.0001
Postoperative hospital stay (days)	21.3 ± 6.4	8.4 ± 2.3	< 0.0001
Surgical mortality	52 (25.4%)	24 (1.8%)	< 0.0001

LCOS indicates low cardiac output syndrome; ARF, acute renal failure; DSWI, deep sternal wound infection; and ICU, intensive care unit.

view of 3523 patients undergoing CABG and/or valve surgery, multivariate logistic regression analysis showed that LCOS was an independent predictor of longer hospital stay and re-admission to the ICU.¹⁴⁾ Higher morbidity and mortality coincided with longer ICU stay and postoperative hospital stay, which might contribute to an increase of the economic impact of this entity. Obviously, it became crucial for clinicians to identify the predictors of LCOS following CABG surgery, in order to optimize pre- and intraoperative risk factors involved in strategies to reduce the incidence of LCOS following CABG.

Through reviewing 1524 consecutive well-documented patients who underwent isolated CABG surgery from January 2010 to December 2013, we identified older age (age > 65 years), impaired left ventricular function (LVEF < 50%), on-pump CABG, emergent CPB, and incomplete revascularization as 5 predictors of LCOS following CABG surgery. The Hosmer-Lemeshow goodness of fit of the statistical model established in this study was 0.91, indicating that the model matched the data very well, therefore, the results were statistically very reliable.

Older age was one of the major risk factors contributing to LCOS following CABG surgery. The incidence of CABG in elderly patients has been increasing.¹⁵⁾ Older age has been documented as a risk factor for LCOS after heart surgery such as mitral valve surgery and aortic valve surgery.^{6,7)} The same type of phenomenon was observed in this study, which specifically addressed isolated CABG surgery. Misare demonstrated an age-dependent sensitivity to myocardial ischemia in an ovine model, introducing the term "senescent myocardium", concluding that elderly patients may be at increased risk for myocardial injury because of their senescent myocardium, and developing higher rates of LCOS after CABG.¹⁶⁾ In addition, CABG patients over 65 years of age often had multiple concurrent diseases, poor cardiopulmonary reserve, and diffuse vascular sclerostenosis. They had a further reduction in their cardiopulmonary performance after CABG with or without cardiopulmonary bypass, and thus were more prone to postoperative LCOS.

Another risk factor for LCOS following CABG in this study was impaired left ventricular function. Impaired left ventricular function is the most important predictor of postoperative morbidity and mortality.^{17,18)} Patients with impaired left ventricular function had a poor cardiac function reserve, which made patients more prone to developing LCOS after experiencing intraoperative myocardial injury.

We have demonstrated on-pump CABG was a predictor of LCOS after isolated CABG. Lower release of enzymes (parameters of myocardial injury) from myocardial injury in the postoperative period in patients undergoing off-pump CABG compared to on-pump CABG was reported, suggesting a lower degree of myocardial injury in off-pump CABG.^{19,20)} The regional normothermic ischemia in off-pump CABG and the temporary interruption of coronary flow approached seemed to cause less myocardial injury compared to hypothermic global ischemia induced by CPB and cardioplegic arrest, which made patients develop smaller rates of LCOS after CABG.²¹⁾

Emergent CPB was also a risk factor for LCOS following isolated CABG. By eliminating the need for cardiopulmonary bypass, off-pump CABG has theoretical clinical advantages over conventional on-pump CABG procedures, and thus was

an attractive option to conventional on-pump CABG. However, due to unstable hemodynamics and ventricular fibrillation when the heart was displaced to expose and then graft a target coronary artery during the CABG procedure, CPB had to be emergently established, and off-pump CABG had to be urgently switched to on-pump CABG. Patients received serious myocardial injury and severe cardiac function damage during this urgent switch procedure, and hence were prone to developing LCOS after experiencing emergent CPB during CABG.

In this study, incomplete revascularization was also identified as a risk factor for LCOS after CABG surgery. Independently of the use or no use of CPB, incomplete revascularization damaged myocardium, and hence was prone to cause LCOS after CABG. The rate of incomplete revascularization in this study was 6.4%, which was lower than that in previous reports.^{11,22)} Our result was consistent with a previous study which stated that incomplete revascularization was an independent risk factor for LCOS following CABG.¹¹⁾

The primary limitation of this study was its retrospective and observational nature, limiting generalization of its results. Another limitation was the lack of detailed data of cardiac output. Cardiac output and cardiac index were not routinely measured perioperatively for each patient in our center.

In conclusion, LCOS following isolated CABG caused higher mortality, higher rates of morbidity in the forms of pulmonary complications, stroke, renal failure and deep sternal wound infection, and longer ICU and postoperative hospital stays; older age (age > 65 years), impaired left ventricular function (LVEF < 50%), on-pump CABG, emergent CPB, and incomplete revascularization were identified as predictors of LCOS following CABG surgery.

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