

Markers of Myocardial Ischemia in the Evaluation of the Effect of Left Anterior Descending Coronary Artery Lesion and Collateral Circulation on Myocardial Injury in 1-Vessel Off-Pump Coronary Bypass Surgery

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ABSTRACT

Background: The purpose of this study was to use serum markers for myocardial tissue damage to evaluate the effect of the severity of left anterior descending artery (LAD) lesions after 1-vessel off-pump coronary artery bypass grafting.

Methods: A consecutive series of 20 patients with a totally occluded LAD and only retrograde filling (group T; n = 10) or critical stenosis (70%-99%) and only antegrade filling (group C; n = 10) were included in this study. One patient in group C who displayed no increases in the levels of markers for myocardial ischemia was excluded from the study because of the intraoperative repetition of the anastomosis. Creatine kinase activity (CK), CK-MB activity, and CK-MB mass, myoglobin, lactate, and cardiac troponin I (cTnI) concentrations were determined in venous blood samples taken immediately before and after the anastomosis and at 4, 8, 12, 24, and 48 hours postoperatively.

Results: There were no perioperative myocardial infarctions. One patient in group T developed low cardiac output syndrome 48 hours after the operation and died after 1 month. His enzyme levels did not increase in the first 2 days postoperatively. Anastomosis times were similar for the T and C groups (6.85 ± 0.9 minutes versus 8.4 ± 2.2 minutes, respectively; $P = .069$). The levels of all cardiac markers except cTnI increased significantly in the first 24 postoperative hours. CK-MB activity, CK-MB mass concentration, and cTnI concentration were not different between the 2 groups. Four patients in each group were evaluated for the patency of the anastomosis, and all control angiography and myocardial scanning tests showed patent anastomoses and no ischemia.

Conclusions: One-vessel off-pump coronary artery bypass grafting can be performed safely in patients with serious LAD stenosis and borderline antegrade blood flow without the need for any coronary collateral circulation support. A short anastomosis time prevents myocardial injury during off-pump coronary surgery.

INTRODUCTION

Off-pump coronary artery bypass grafting (CABG) procedures have been developed to avoid cardiopulmonary bypass and cardioplegia with global cardiac arrest. Cardiopulmonary bypass induces an inflammatory response with activation of leukocytes [Edmunds 1998], which injures the myocardium and coronary endothelium during reperfusion [Okazaki 2000]. It has been well shown that off-pump CABG is less invasive in terms of the reduction in myocardial injury associated with cardiopulmonary bypass [Wan 1999]. This result has been verified by observations of lower levels of release for specific markers of myocardial injury [Ascione 1999, Kilger 2000] and angiographic results that did not worsen [Omeroglu, 2000]. In addition, we recently reported that 1-vessel off-pump CABG had a better outcome than conventional CABG in patients with left ventricular dysfunction [Kırallı 2002].

In the last several years, a great deal of equipment has been developed to reduce the minor myocardial injury that occurs during off-pump CABG. Several mechanical coronary artery stabilizers are used during coronary anastomosis. To achieve bloodless anastomotic areas during off-pump coronary surgical procedures, cardiac surgeons have preferred different techniques. The most useful technique is coronary clamping and gas insufflation; however, the possibility of coronary artery endothelial injury related to the snaring of the coronary artery or bulldog clamping and gas insufflation during coronary anastomosis has always been the most feared disadvantage. Using elastic sutures and humidified gas insufflation is a choice with less potential for harm in off-pump coronary surgery [Okazaki 2001]. The other choice is to use an intraluminal shunt during coronary anastomosis in off-pump CABG to obtain continuity in coronary blood flow [Rivetti 1997]. However, although intraluminal shunts prevent hemodynamic deterioration during off-pump CABG [Yeatman 2002], their use is not widespread. A more cautious approach may be to use intraluminal shunts selectively because of the possibility that their use will injure the endothelium [Puskas 2002].

There is no any report in the literature that has investigated the effect of the severity of left anterior descending artery (LAD) stenosis and coronary collateral blood flow on myocardial damage in off-pump CABG. Therefore, the purpose of this study was to evaluate myocardial damage, as indicated by

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Demographic Data*

Measurement	Group T (n = 10)	Group C (n = 9)	P
Age (range), y	55.8 ± 11.3 (36-72)	53 ± 14.5 (30-74)	.64
Body weight (range), kg	76.1 ± 10.7 (57-88)	70.5 ± 16.8 (46-104)	.4
Sex M/F, n	9/1	7/2	.45
Risk factors			
Smoking, n	4 (40%)	2 (22.2%)	.37
Hypertension, n	3 (30%)	2 (22.2%)	.56
Diabetes mellitus, n	0	2 (22.2%)	.2
COPD, n	5 (50%)	1 (11.1%)	.09
Family history, n	5 (50%)	3 (33.3%)	.39
Peripheral arterial disease, n	1 (10%)	1 (11.1%)	.74
Cerebrovascular disease, n	1 (10%)	0	.53
Cardiac parameters			
Previous myocardial infarction, n	9 (90%)	6 (66.6%)	.25
Previous PTCA/stent, n	1 (10%)	2 (22.2%)	.45
Angina pectoris, Canada class	2.8 ± 0.8	2.3 ± 1	.3
LAD diameter, mm	1.6 ± 0.2	1.5	.2

*Data are expressed as the mean ± SD where appropriate. M indicates male; F, female; COPD, chronic obstructive pulmonary disease; PTCA, balloon angioplasty; LAD, left anterior descending artery.

serum levels of creatine kinase (CK) isoenzymes, cardiac troponin I (cTnI), and myoglobin release, after 1-vessel off-pump CABG without the use of intracoronary shunts.

PATIENTS AND METHODS

Study Design

After institutional review board approval and written informed consent was obtained, 20 consecutive patients with 1-vessel coronary artery disease and scheduled for surgical revascularization were enrolled in this prospective study between October 2001 and January 2002. The patients were divided into 2 groups according to their LAD lesion. All LADs in group T (n = 10) were totally occluded before the first diagonal branch, and the distal vessel bed was visualized to be retrograde by the collateral branches between the right coronary artery and the LAD. All LADs in group C (n = 10) had critical isolated stenosis (a 70%-99% narrowing in the luminal diameter) in the proximal segment, and the distal segment was filled antegrade by aortic ejection but was not visualized retrograde by the collateral branches. Preoperative characteristics are shown in the Table.

Indication for CABG

The indication for surgical treatment was influenced by the morphologic characteristics of the LAD lesions, a viable myocardium, and unsuitability of the patient for balloon angioplasty. Exclusion criteria included the intraoperative repetition

of the anastomosis, a longer anastomotic duration (>15 minutes), any arrhythmia, and a postoperative myocardial infarction as indicated by electrocardiography or significant increases in the levels of cardiac enzymes in the first 48 hours after surgery. No exclusion criteria were applied with respect to the anatomic position or size of the LAD. This design was chosen to demonstrate only the influence of the continuity of coronary blood backflow and the presence of collateral circulation.

Anesthesia and Anticoagulation Therapy

Standard anesthesia technique was used for all patients and consisted of oral premedication (10 mg diazepam) the night before surgery and an intramuscular injection of the same dose 1 hour before induction, followed by totally intravenous anesthesia (3 mg/kg per hour propofol combined with 10-20 µg/kg fentanyl). Neuromuscular blockade was achieved by administering pancuronium (0.15 mg/kg). After the induction of anesthesia, a double-lumen central venous catheter was inserted into the right internal jugular vein. In accordance with our protocol [Kıralı, 1999a], patients routinely received 5000 IU heparin after the harvesting of the left internal mammary artery (LIMA) to obtain a target activated clotting time of ≥200 seconds. We did not reverse the heparin effect at the completion of the surgical procedure if reversal was unnecessary [Omeroglu, 2000].

Surgical Procedures

All procedures were performed through a median sternotomy. The pericardium was opened at the level of the proximal ascending aorta with the incision extending to the diaphragm, and the pericardium was retracted with 0-silk sutures. Two or 3 gauze swabs were inserted under the heart to achieve better visualization of the LAD. The heart rate was slowed to less than 80 beats/min with a β-blocker. Two patients in group C, however, required the use of a mechanic coronary artery stabilizer. After exposing and stabilizing the target vessel, we prepared the LAD for the arteriotomy. We placed a bulldog clamp 1 cm proximal to the intended target site and occluded the vessel throughout the anastomosis. We did not use distal clamping or intraluminal shunts in any patient. We performed all anastomoses with a single 7/0 propylene suture and a continuous suture technique. We used an air-blowing system of our own design to obtain a bloodless area [Ipek 1996]. Before we tied the suture at the end of the anastomosis, we opened the proximal bulldog clamp and then removed the LIMA bulldog clamp. Finally, the blood flow from the proximal LAD and then the LIMA was checked.

Measurements

Measurements of the catalytic activities of CK and CK-MB in the serum were determined with commercial reagents in an automated chemical analyzer (Konelab 60i; Thermo Clinical Lab Systems, Vantaa, Finland). CK-MB mass, cTnI concentration, and myoglobin concentration were assayed by means of a fluorescent sandwich enzyme immunoassay using the Triage Cardiac Panel (Biosite Diagnostics, San Diego, CA, USA), as detailed by Ng and associates [Ng 2001]. The upper reference limits for the normal range were set as follows:

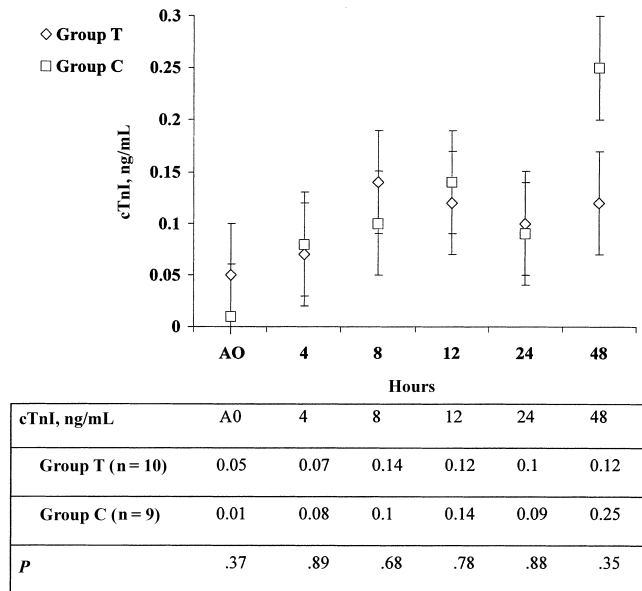


Figure 1. Comparison of mean cardiac troponin I (cTnI) levels for both groups. Measurements were made before and after anastomosis (AO) and at 4, 8, 12, 24, and 48 hours after the off-pump coronary artery bypass grafting operation.

CK, 225 U/L; CK-MB activity, 25 U/L; CK-MB mass concentration, 9 ng/mL; myoglobin, 170 ng/mL (the maximal value is 500 ng/mL); and cTnI, 1 ng/mL. CK activity, CK-MB activity, and CK-MB mass, myoglobin, and cTnI concentrations were determined in venous blood samples immediately before and after anastomosis and at 4, 8, 12, 24, and 48 hours postoperatively.

Statistical Analysis

A commercial statistical software package (SPSS for Windows, version 10.0; SPSS, Chicago, IL, USA) was used for data analysis. Data are presented as the mean $\pm$ SD. Differences between categorical variables were tested by means of the χ^2 and the Fisher exact tests, analysis of variance and the unpaired *t* test were used to compare the means of serum marker levels in the 2 groups, and differences between continuous variables were tested with the paired *t* test, the Wilcoxon signed rank test, and the Mann-Whitney *U* test. A *P* value of less than .05 was considered statistically significant.

RESULTS

One patient in group C was excluded from the analyses because of the intraoperative repetition of the anastomosis. The first anastomosis was performed in 12 minutes but had to be repeated because of technical problems. The patient did not exhibit any electrocardiogram changes or experience any hemodynamic deterioration. Another patient in group T exhibited hemodynamic deterioration after the second postoperative day (>48 hours), and low cardiac output syndrome developed. The patient was reintubated and received an intra-aortic balloon pump and inotropic support, but he died on day

30. We did not exclude this patient from the study, because his enzyme levels did not increase in the first 48 hours and there were no electrocardiogram changes during this period.

Operative Data

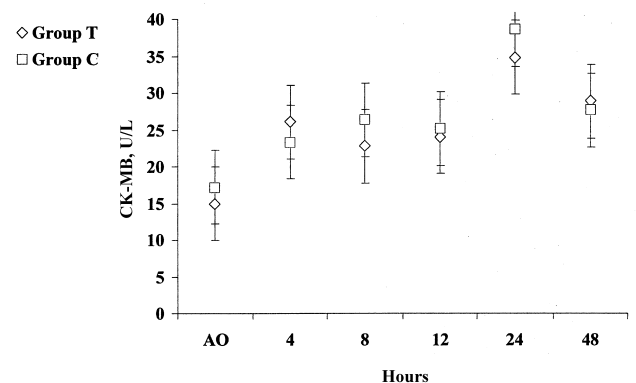
The occlusion times for LAD were 6.85 ± 0.94 minutes (range, 5.5–8 minutes) in group T and 8.44 ± 2.19 minutes (range, 6–12 minutes) in group C (*P* = .069). The differences in extubation times and lengths of stay in the intensive care unit (ICU) and hospital for groups T and C were statistically insignificant. The mean extubation time was 8.7 ± 3.3 hours for group T versus 8.3 ± 1.7 hours for group C (*P* = .71); the mean ICU stay was 42 ± 17.1 hours versus 41 ± 11.2 hours (*P* = .89); and the mean hospital stays were 5.2 ± 1.3 days versus 5.4 ± 2.2 days (*P* = .78).

Postoperative Complications

There were no electrocardiogram changes during the LIMA-LAD anastomoses or in the ICU. There were no cases of lethal arrhythmia. Atrial fibrillation (4 cases) was the only rhythm problem observed during the early postoperative period in the ICU, and it returned to the sinus rhythm after medical management during the first 24 hours following surgery. Postoperative drainage in group C was higher than in group T (705.5 ± 345 mL and 460 ± 196.9 mL, respectively), but the difference was not statistically significant (*P* = .084). There were no cases of reexploration for bleeding, of infection, or of peripheral or cerebral embolic events.

Markers of Myocardial Injury

The serum levels of the specific markers of myocardial injury, cTnI (Figure 1), CK-MB activity (Figure 2), and



CK-MB activity, U/L	A0	4	8	12	24	48
Group T (n = 10)	15	26.1	22.8	24.1	34.8	28.9
Group C (n = 9)	17.2	23.3	26.4	25.2	38.6	27.7
<i>P</i>	.29	.4	.31	.77	.52	.8

Figure 2. Comparison of mean creatine kinase MB (CK-MB) activity levels for both groups. Measurements were made before and after anastomosis (AO) and at 4, 8, 12, 24, and 48 hours after the off-pump coronary artery bypass grafting operation.

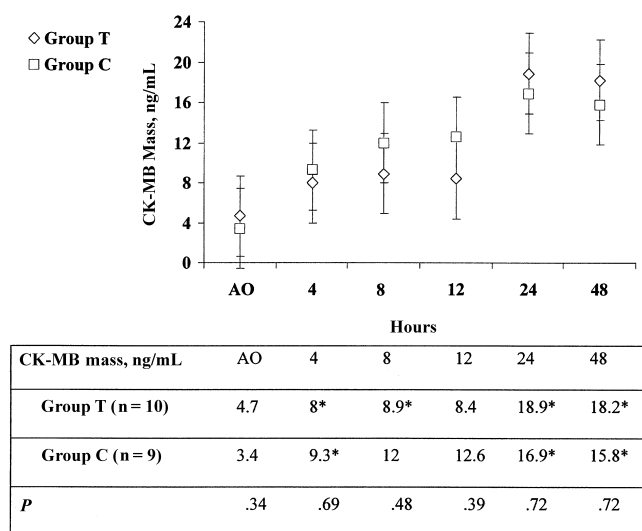


Figure 3. Comparison of mean creatine kinase MB (CK-MB) mass levels for both groups. Measurements were made before and after anastomosis (AO) and at 4, 8, 12, 24, and 48 hours after the off-pump coronary artery bypass grafting operation. * indicates level significantly increased in the same group after the operation ($P < .05$).

CK-MB mass (Figure 3), for the 2 groups did not differ throughout the entire measurement period ($P > .05$). The cTnI level did not exceed the upper reference limit in both groups. After 24 hours, the maximal CK-MB activity values were 34.8 ± 15.8 U/L in group T and 38.6 ± 8.1 U/L in group C. Maximal CK-MB mass concentrations were measured 24 hours postoperatively in the T and C groups (18.9 ± 10.7 ng/mL and 16.9 ± 12.4 ng/mL, respectively).

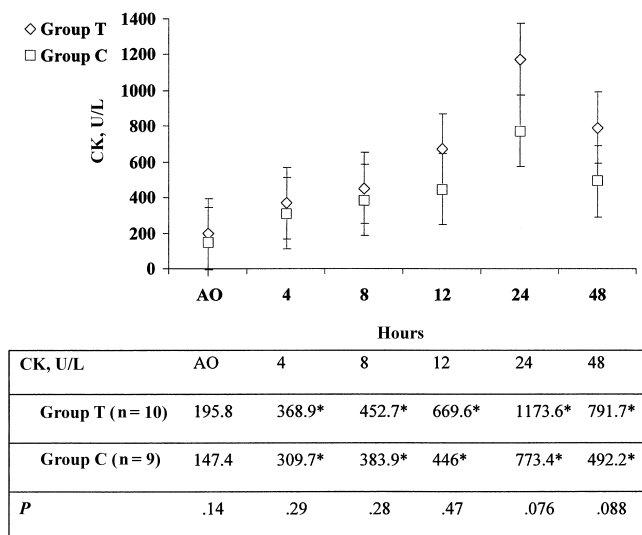


Figure 4. Comparison of mean creatine kinase (CK) levels for both groups. Measurements were made before and after anastomosis (AO) and at 4, 8, 12, 24, and 48 hours after the off-pump coronary artery bypass grafting operation. * indicates level significantly increased in the same group after the operation ($P < .05$).

The maximum CK activities were reached at 24 hours postoperatively in groups T (2229 U/L) and C (1093 U/L). Maximal values for CK activity were mostly observed in group T. CK activity (Figure 4) was significantly higher in group T at only 12 hours postoperatively (669.6 ± 282.9 U/L versus 446 ± 150.4 U/L; $P = .047$).

Myoglobin concentrations (Figure 5) were higher in group T, but the difference never reached statistical significance ($P > .05$). Myoglobin concentrations exceeded 200 ng/mL before and after LAD-LIMA anastomosis in 16 patients (the levels in 2 patients in group C and 1 in group T did not), and except for 1 patient, the myoglobin concentration did not decrease below this level before 48 hours postoperatively. After 12 hours, maximal myoglobin values were recorded in group T (>500 ng/mL) and group C (434 ± 132.4 ng/mL).

Angiographic Results

We performed control angiography and myocardial scanning of 4 randomly selected patients in each group at the second postoperative month. All LAD-LIMA anastomoses were found to be patent, and thallium scintigraphy showed that the ischemia had improved.

COMMENT

After off-pump CABG was shown to perform as well as the conventional technique in selected patients, cardiac surgeons have tried to develop equipment more suitable for off-pump coronary surgery, because the quality of the coronary anastomosis and hemodynamic situation of off-pump CABG is still a great concern. Okazaki and associates [Okazaki 2001] reported that coronary artery snaring with elastic sutures and

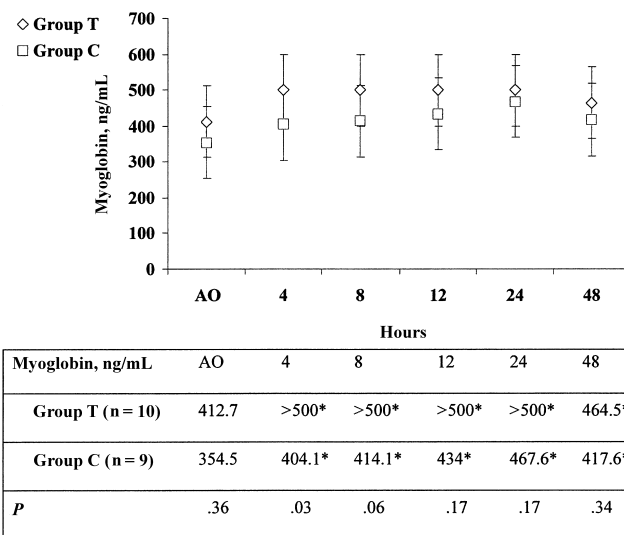


Figure 5. Comparison of mean myoglobin levels for both groups. Measurements were made before and after anastomosis (AO) and at 4, 8, 12, 24, and 48 hours after the off-pump coronary artery bypass grafting operation. * indicates level significantly increased in the same group after the operation ($P < .05$).

humidified gas insufflation did not cause coronary endothelial injury. Yeatman and associates [Yeatman 2002] reported that using intraluminal coronary shunts had the beneficial effects of preserving intraoperative myocardial function during off-pump coronary surgery in patients with 3-vessel coronary artery disease. We have reported that midterm angiographic results for off-pump CABG is no worse than results involving conventional techniques [Omeroglu, 2000]. In addition, minimally invasive CABG via left anterior limited thoracotomy does not influence outcome and cause worse angiographic results [Kırali, 1999b]. We have performed more than 2500 procedures on the beating heart since 1993 in cases of single or multiple-vessel disease, and we can conclude from this experience that the results achieved with LAD-LIMA anastomosis and off-pump technique are as good as those obtained with conventional techniques. We usually prefer not to use any myocardial wall stabilizer for the LAD or the right coronary artery, because it can cause some technical difficulties and injure the myocardium. We may use a stabilizer when the heart rate is higher than 80 beats per minute or if the LAD is intramyocardial or embedded in fat. We never perform off-pump coronary surgery on patients with a LAD having multiple lesions, a small diameter (<1.5 mm), or any calcification. We use proximal coronary artery snaring or bulldog clamping for coronary occlusion and use gas insufflation to clear the anastomotic site, but we never apply distal clamping. On the other hand, an intraluminal shunt can damage the endothelium and requires more time to complete. In the present study, the mean anastomosis time was shorter than 8.5 minutes (maximum duration, 12 minutes), which reflects our standard LIMA-LAD anastomosis time on the beating heart. This anastomosis duration does not need any intraluminal shunt to maintain coronary blood flow. However, if we think that a LIMA-LAD anastomosis will take more than 15 minutes, we usually prefer to use a conventional technique.

Cardiac troponin I has been suggested to be a highly specific indicator of myocardial cell damage [Birdi 1997a]. A moderate postoperative elevation in cTnI level indicates reversible minor myocardial damage in most patients undergoing CABG [Carrier 2000]. Eigel and associates [Eigel 2001] found that a cTnI level of 0.91 ng/mL was correlated with an adverse outcome. Birdi and associates [Birdi 1997b] suggested that the ischemic injury to the myocardium as indicated by cTnI release might not be important after an occlusion of the LAD as part of a left anterior small thoracotomy procedure. Increases in CK and myoglobin levels not only indicate myocardial damage but also can increase because of transmuscular surgical access [Inselmann 1998]. In the present study, cTnI did not reach significantly elevated levels (1 ng/mL) in any patient throughout the entire measurement period. The levels of all other enzymes increased after the operation.

The second aim of this study was to investigate how the heart with a critical LAD lesion would be affected during the off-pump procedure when there was no coronary collateral circulation. Are the levels of LAD stenosis and collateral flow important in preventing myocardial injury during the off-pump CABG procedure? If they are, after the occlusion of the LAD with a critical lesion and without a collateral circu-

lation, the myocardium will be deprived of blood supply because the distal bed of the LAD will receive no blood flow, and this lack of flow may cause serious myocardial damage. The anterior left ventricular wall with critical LAD lesions and antegrade coronary blood flow is on the borderline of being protected from ischemia and can be damaged when the LAD is occluded during the off-pump procedure. On the other hand, hearts with a totally occluded LAD and retrograde blood flow are not affected by occlusion of the LAD, because the collateral blood flow does not change and the myocardium takes blood and other elements from the collaterals. Transient minor myocardial damage does not worsen the early outcome and does not cause any electrocardiogram changes or hemodynamic deterioration. Occlusion of the coronary blood flow can be well tolerated during anastomosis, when anastomosis takes less than 12 to 15 minutes and causes no release of cTnI. In the present study, we could not show that retrograde blood flow from collateral arteries had a better effect in preventing myocardial injury during off-pump CABG in patients with isolated LAD lesions. Because we did not observe any difference between the groups, we suggest that LAD-LIMA anastomosis with the off-pump technique is not affected by coronary collateral circulation if the surgical procedure does not take more time.

In conclusion, a LAD with a critical lesion can be revascularized with off-pump CABG, as well as with the conventional technique, and this strategy does not worsen the early outcome because of the absence of collateral coronary artery circulation. Based on our extensive experience with this procedure, we propose that to be safe the duration of an LAD-LIMA anastomosis on the beating heart must not exceed 15 minutes. The data for cTnI release indicate that an anastomosis taking a shorter time with the off-pump coronary surgical procedure does not cause any ischemic injury to the myocardium.

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