Myocardial injury during off-pump surgery

The effect of intraoperative risk factors

Bulend Ketenci, *MD,* ***Yavuz Enc,*** *MD,* ***Batuhan Ozay,*** *MD,* ***Serdar Cimen,*** *MD,* ***Rafet Gunay,*** *MD,* ***Gokcen Orhan,*** *MD,* ***Onur Gurer,*** *MD,* ***Alper Gorur,*** *MD,* ***Onder Teskin,*** *MD,* ***Mahmut M. Demirtas,*** *MD.*

ABSTRACT

الأهداف: لم يتم تحديد العوامل المؤثرة أثناء العملية الجراحية التي تساهم في إصابة نقص التروية لعضلة القلب خلال عملية القلب بدون استخدام مضخة القلب الاصطناعي. يتم استعمال تروبونين تي (سي تي ان تي) حالياً لتقييم إصابة عضلة القلب. لتحقيق أفضل النتائج، يجب تخفيض درجة إصابة عضلة القلب خلال إجراء عملية القلب بدون استخدام مضخة القلب الاصطناعي. لقد قمنا بدراسة العوامل التي تصف ترتيب جدول المرضى لعملية القلب بدون استخدام مضخة القلب الاصطناعي القابلة لإصابة عضلة القلب.

الطريقة: قبل العملية قمنا بفحص ١٢٣ مريضاً أجريت له عملية جراحية بواسطة مجموعة من الجراحين بدون استخدام تقنية مضخة القلب الاصطناعي في الفترة ما بين يناير ٢٠٠١م الى يونيو ٢٠٠٦م بمركز سيامي ارسيك للجراحة الصدرية والقلب الوعائي. تم تقييم ظهور إصابة عضلة القلب خلال العملية الجراحية بواسطة قياسات (سي تي أن تي) بعد العملية الجراحية. بعد ذلك، تم تقييم الصلة بين العوامل قبل وبعد العملية الجراحية إحصائياً.

النتائج: تم أخذ عينات الدم من أجل قياسات (سي تي ان تي) من جميع المرضى قبل العملية. ومباشرة بعد الوصول الى وحدة العناية المركزة، ثم بعد ست ساعات و١٢ ساعة و٢٤ ساعة بعد إعادة فتح الأوعية القصية. عندما يكون الأمر عائداً الى عوامل الخطر أثناء العملية الجراحية، وجدنا أن معدل ضربات القلب وضغط الدم ووقت المفاغرة هي العوامل الرئيسية المحددة لإصابة خلية عضلة القلب والتي تظهر أثناء عملية القلب بدون استعمال مضخة القلب الاصطناعي.

خاتمة: على الرغم من عدم استخدام مشابك عرضية للأورطي وإيقاف القلب في عملية إعادة فتح الأوعية لعضلة القلب بدون استعمال مضخة القلب الاصطناعي،كان تلف خلية عضلة القلب نتيجة لنقص التروية أمراً محتوماً أيضاً في تقنية عملية القلب بدون استعمال مضخة القلب الاصطناعي. لذلك، تعد معالجة معدل نبض القلب وتقلص عضلة القلب مرغوبة ليست فقط بسبب المفاغرة الدقيقة ولكن أيضاً من أجل حماية عضلة القلب خلال إجراء عملية القلب بدون استعمال مضخة القلب الاصطناعي.

Objective: To achieve better outcomes, the degree of myocardial injury due to off-pump coronary artery bypass surgery (OPCAB) must be reduced. We studied the factors that render patients scheduled for OPCAB vulnerable to myocardial injury, using troponin T (cTnT) as a marker of myocardial injury.

Methods: We prospectively investigated 123 patients being operated by a group of surgeons with off-pump technique between January 2001 and June 2006 in Siyami Ersek Thoracic and Cardiovascular Surgery Center. Myocardial injury occurring during surgery was assessed by post-operative cTnT measurement. Then, the relation between intraoperative factors and postoperative cTnT release were statistically evaluated.

Results: Blood samples for cTnT measurement were taken from all patients before operation, immediately after arrival at the intensive care unit, then at 6, 12, and 24 hours after distal revascularization. When regarding the intraoperative risk factors, we found that the heart rate, blood pressure and anastomosis time are the main determinant of myocardial cell injury occurring during OPCAB surgery.

Conclusions: Although aortic cross-clamp and cardioplegic arrest were not used in off-pump myocardial revascularization, the ischemic myocardial cell destruction was also inevitable in off-pump technique. Therefore, management of heart rate and myocardial contractility was desirable not only for precise anastomosis but also for myocardial protection during OPCAB surgery.

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From the Department of Cardiovascular Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Center, Istanbul, Turkey.

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Address correspondence and reprint request to: Dr. Bulend Ketenci, Gazi Muhtar Pasa Korusu Mazhar Osman Sk. 25/4 Feneryolu, Kadıköy, Istanbul, Turkey. Fax. +902 (16) 6146276. E-mail: bulendketenci@gmail.com

Cardiopulmonary bypass (CPB) has been the conventional technique of coronary bypass surgery, enabling a bloodless and still heart setting to perform a safe operation. However, well-evidenced detrimental side effects of cardiopulmonary circuit on whole body systems have always created tediousness and myocardial preservation techniques have never been absolutely perfect. Recently, innovative cardiac stabilization techniques have regained interest enabling cardiac operations performed on beating hearts. While damaging effects of cardiopulmonary circuit and aortic cross clamping have been avoided, only the coronary perfusion of the revascularized target vessel has been interrupted. Serious concerns have risen on the potential risk of ischemic damage to the metabolically active myocardium during vessel occlusion. Therefore, the management of metabolically active heart is the most important aspect of off-pump coronary artery bypass surgery (OPCAB). This is the main disadvantage of OPCAB, which is the potential for acute and disastrous hemodynamic instability requiring immediate conversion to CPB.[1] The risk of hemodynamic compromise during OPCAB surgery mainly resulted from retraction and stabilization of the heart. However, occlusion of coronary artery during coronary anastomosis while the heart beats also causes an inevitable myocardial injury during surgery and contributes to the hemodynamic compromise. Intracoronary shunt improves visualization by providing a bloodless field for anastomotic suturing, while at the same time providing flow through the anastomotic site to the myocardium. The pattern of flow is turbulence through intracoronary shunt, laminary flow is fairly poor. This shows the perfusion of the distal coronary bed can not be good.[2] Coronary flow can be lessened despite the use of intracoronary shunt during the anastomosis. As myocardial injury always persists during OPCAB surgery, the intraoperative factor that contributes to myocardial ischemia should be identified clearly to avoid possible complications related to the operation. Troponin T (cTnT) is currently used to assess myocardial injury, cTnT has been established as a sensitive marker for the detection of major and minor myocardial cell injury.[3] Troponin T has the advantage of a broad diagnostic window of up to 14 days and has been shown to be a marker for minor myocardial cell damage. There has been a revolution in the technology for cardiac marker measurement description of the measurement of cTnT. The advantage of cTnT lies in its ability to provide a cardio specific diagnosis. A specific and sensitive method for detection of preoperative myocardial ischemic injury is at present unavailable. There is evidence that marginal serum cTnT elevation is related to the prognosis of patients with ischemic heart disease.[4] To achieve better outcomes, the degree of myocardial injury due to OPCAB must be reduced. We studied the factors that render patients scheduled for OPCAB vulnerable to myocardial injury, using cTnT as a marker of myocardial injury.

Methods. Off-pump coronary artery bypass surgery surgery with modern stabilizers had been used as alternative method to conventional coronary artery bypass graft surgery (CCABG) for the last decade in our center. At the beginning, OPCAB procedure was performed only in selected patients especially for isolated left anterior descending (LAD) coronary artery lesions. With growing surgical experience, indication for OPCAB has been changed and patients with multi-vessel grafts can now be a candidate for OPCAB. Although circumflex and right systems revascularization is not considered as a contraindication for off pump surgery we did not include these cases in this trial. As hemodynamic changes that commonly occur during repositioning and stabilization of the heart are common during circumflex and right systems revascularization.[5] For this reason, we included the patients in our study that cannot be suitable for PCI and revascularized for only LAD disease. As the biochemical markers that we measured could be affected, single vessel patients that had additional pathology were excluded from the study group. Patients in which incomplete revascularization was performed due to diverse reasons were not included in this study either. (Troponin levels may also be elevated with acute or chronic conditions such as myocarditis (heart inflammation), congestive heart failure, severe infections, kidney disease, dermatomyositis, and polymyositis). The study protocol was approved by the institutional review board (Ethical Committee) and was consistent with the principles of the Declaration of Helsinki. Written consent were obtained from all study participants. We have prospectively investigated 123 patients (**Table 1**) being operated by a group of surgeons with off-pump technique between January 2001 and June 2006 in Siyami Ersek Thoracic and Cardiovascular Surgery Center. Ninety-six of them were males and 27 were females. The mean age was 52.35 ± 3.32 years. No known additional disease such as diabetes mellitus, hematological or renal disorder was ever present in any case.

Operative technique. Routine beta-blocker was prescribed preoperatively to all patients unless contraindicated. Cardiac output was continuously monitored using a continuous output Swan-Ganz catheter (Vigilance; Edwards Life Sciences, Irvine, CA, USA). Conventional median sternotomy was the standard exposure technique. Following pericardial stay sutures, target coronary arteries were explored. Routine heparin of approximately 5000 units was administered

following exposure and decision of keeping on off-pump surgery. Octopus-III (Medtronic, Minnesota, USA) was then replaced to further immobilize the vessel. Proximal and distal stay sutures were then snared before arteriotomy to diminish bleeding and to obtain a bloodless field. Intracoronary shunt (Medtronic, Inc, Minneapolis, Minn) was placed after the arteriotomy, proximal and distal snares were opened so the flow of the coronary artery was allowed. Heparin was not reversed with protamin in any case. Blood samples were taken from all patients before operation (T0), immediately after arrival at the intensive care unit (ICU) (T1), then at 6 (T6), 12 (T12), and 24 (T24) hours after distal revascularization. In all patients, electrocardiographic and hemodynamic follow-up was established concomitantly with enzymatic take-offs. Enzymatic measurements were performed with Tosoh AIA system analyzer using immunoenzymatic technique for cardiac troponin T (cTnT). A new Q-wave or 25% decrease of size in R-wave in 2 following derivation was evaluated as transmural myocardial infarct and ST elevation in at least 2 derivations and negative T was evaluated as subendocardial ischemia in electrocardiogram (ECG). The intraoperative factors that are related to myocardial injury were heart rate and mean systemic blood pressure called as double product and the anastomosis time. They were clearly determined in each patient. (mean hour per minute and mean systemic blood pressures were recorded during each anastomosis) Then, the relation between postoperative cTnT levels and double product and occlusion time during anastomosis were statistically evaluated.

Statistical analysis. Data are given as mean values ± standard deviation and categorical data were reported as percentages. We used JMP (John's Macintosh Project) software (version 5.01, SAS Institute Inc.) for statistical analysis. As the serum cTnT values at 6 and 24 hours were not normally distributed, the Spearman's correlation coefficient (rs) was computed and then, T6 and T24 levels were analyzed by using Wilcoxon test.[6] Significant differences were considered to exist when calculated p values were less than 0.05.

Results. ***Operative data.*** Left internal thoracic artery (LITA) was used in 122 cases to revascularize LAD. Left anterior descending artery revascularization was performed with a saphenous vein graft in only one patient. Mean anastomosis time per anastomosis was 16 ± 2.8 minutes. The clinical characteristics of the patients were summarized in **Table 1**. All patients were discharged from cardiovascular ICU on the first day of operation and all were discharged from the hospital on the 4th or 5th day of operation. Bleeding revision was needed only in one patient however, no changes in the

Table 1 - Preoperative, peroperative and postoperative patients characteristics.

Characteristics	Patients (mean±SD)
Preopearative	
Mean age (years)	52.3 ± 3. 3
No. of males	96
No. of single vessel disease	123
Previous myocardial infarction (%)	18 (14.6)
Left ventricular diastolic diameter/ body surface area (mm/m^2)	30.5 ± 4.0
Degree of mitral regurgitation (%)	
None	101 (82.1)
1 out of 4 to 2 out of 4	22 (17.8)
3 out of 4 to 4 out of 4	-
Peroperative	
Peroperative cardiac index	2.50 ± 0.44
Mean heart rate per min during anastomosis	77.1 ± 15.29
Mean systemic blood pressure during anastomosis, (mm Hg)	57.73 ± 10.76
Time required for anastomosis (minutes)	16 ± 2.8
Product of blood pressure and heart rate during anastomosis	4908.12 ± 1763.59
Postoperative	
Mean entubation time (hour)	12 ± 4
Mean unit of blood usage	0.9
Atrial fibrillation (n)	6
Intensive care unit stay (day)	1
Hospital stay (day)	4 ± 2

Table 2 - Relationship between serum cardiac troponin T (cTnT) levels and the indicated factors.

Indicated factors	cTnT at 6 hour		cTnT at 24 hr	
	P-value	rs	*P*-value	rs
Age	0.649	0.06	0.440	0.102
Previous myocardial infarction	0.109	-	0.331	-
Cardiac index	0.65	-0.10	0.77	0.06
Degree of mitral regurgitation	0.38	-	0.14	-
Blood pressure during anastomosis	0.014†	0.384	0.0001†	0.762
Heart rate during anastomosis	0.033†	0.338	0.001†	0.489
DP	0.003†	0.263	0.0001†	0.822
Anastomosis time	0.009†	0.234	0.0001†	0.569

rs - Spearman's correlation coefficient, DP - product of blood pressure and heart rate during anastomosis, †p<0.05

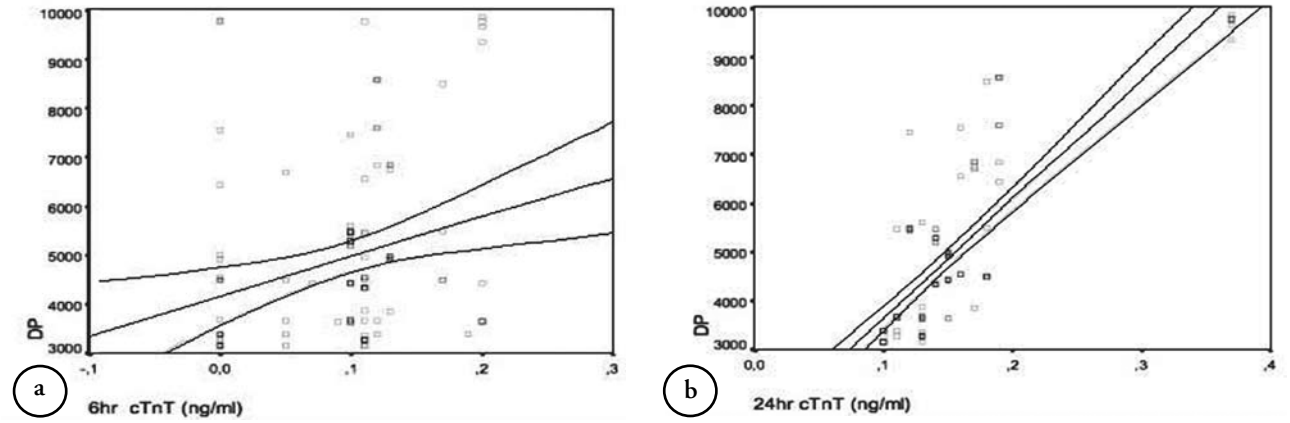

Figure 1 - The serum cardiac troponin T (cTnT) level at **a)** 6 hours [the rs value was 0.263 (p=0.003)] and **b)** 24 hours [The rs value was 0.822 (p=0.0001)] were correlated with the double product during anastomosis. DP - double product

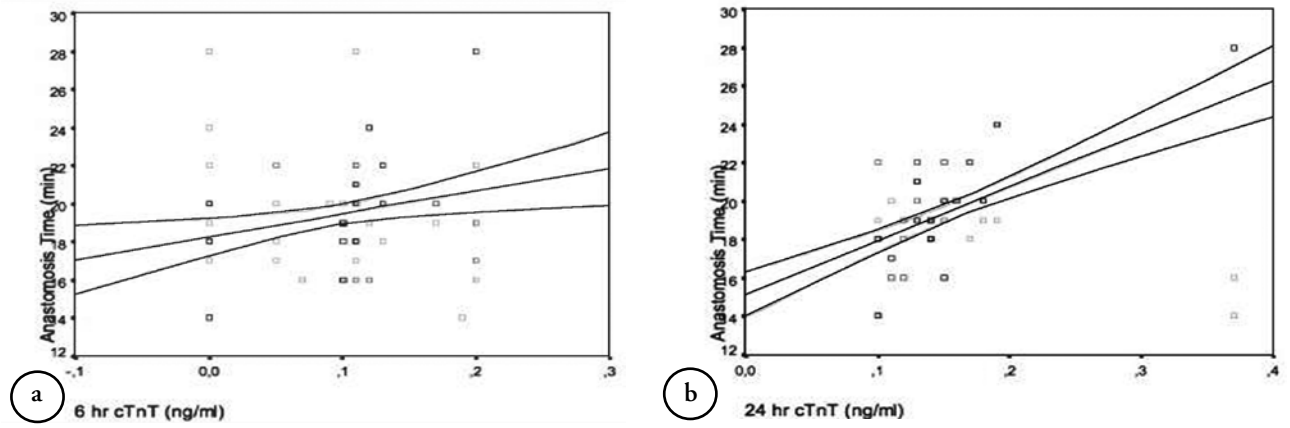

Figure 2 - The serum cardiac troponin T (cTnT) level at **a)** 6 hours (the rs value was 0.234 and p=0.009) and **b)** 24 hours (the rs value was r= 0.569 and p=0.0001) were correlated with the anastomosis time.

ICU stay and hospital discharge period. No patient had ECG and clinical evidence of myocardial damage.

Cardiac troponin T. The absence of serum cTnT was confirmed preoperatively. Patient's age, previous myocardial infarction, cardiac index (CI), degree of mitral regurgitation, were not associated with serum cTnT levels (**Table 2**). The cTnT levels at 6th and 24th hour after operation were used to determine the relation between intraoperative factors and myocardial injury. The serum cTnT level at 6 hours was correlated with the product of mean systolic blood pressure and mean heart rate (double product) during anastomosis (**Figure 1**). The rs value was 0.263 (p=0.003). The heart rate during anastomosis and mean systolic blood pressure were also correlated with serum cTnT levels (**Table 2**). The serum cTnT level at 24 hr correlated with the double product (**Figure 1**). The rs value was 0.822 (p=0.0001). There was also significant relation between the anastomosis time and cTnT release at 6th and 24th hour (rs=0.234 and p=0.009 / rs=0.569 and p=0.0001) (**Figure 2**). Based on the correlation matrix we obtained, mean blood pressure during anastomosis, heart rate during anastomosis, the double product and occlusion time were candidate risk factors for intraoperative myocardial injury. When double product was increased during anastomosis, cTnT level had also been increased that showed the degree of myocardial ischemia during postoperative period. Therefore, double product is the main determinant of myocardial cell injury occurring during OPCAB surgery (**Table 2**).

Discussion. Our results demonstrated that myocardial injury in OPCAB surgery was also inevitable as occurred in CCABG. However, management of myocardial injury during OPCAB surgery is much easier. Insertion of intracoronary shunts had been used

in coronary artery bypass grafting surgery since 1975.[7] An intracoronary shunt is often used to maintain distal perfusion during OPCAB grafting. Studies of the effects of intracoronary shunts on the endothelium of porcine coronary arteries have demonstrated deleterious consequences on endothelium-dependent reactivity,[8] due to the rubbing of the shunt on the endothelial layer. Distal endothelial lesions and dysfunction are particularly worrisome as they may involve the distal run-off of the bypass. Most patients who undergo coronary artery bypass surgery probably have a significant endothelial dysfunction of their coronary arteries associated with advanced atherosclerosis,[9] additional injury to the endothelium from devices may not contribute to the progression of disease within the vessel wall unless the smooth muscle cell layer is injured. Intraluminal shunts aim to achieve hemostasis at the arteriotomy site and to allow antegrade flow to provide myocardial protection. There are unresolved issues regarding whether shunts have a clinical benefit, do provide adequate flow to provide myocardial protection, and whether they cause significant endothelial damage. The potential advantages of OPCAB include reduced systemic inflammation, coagulopathy, atheroembolism, brain edema,[10,11] and respiratory and other end-organ dysfunction. There are also potential economic benefits including reduced postoperative patient instability and faster recovery rates.[10,12-14] Inflammatory cascade inducted by cardiopulmonary bypass circuit releases several cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin–8 (IL-8) that causes myocardial dysfunction.[10] Recent myocardial protection techniques do not absolutely prevent myocardial injury in patients undergoing open-heart surgery especially in patients with high cardiac risk factors.[15-16] On the other hand, off-pump surgery is believed to avoid these side effects. Although off-pump coronary revascularization is an old technique performed first in 1964, there has been renewed interest in performing CABG without cardiopulmonary bypass (CPB) in 1985 by Buffolo et al[15] and Kolessov.[17] The main idea was to operate the patients who could not be operated by conventional methods due to high risks such as severe ventricular dysfunction, chronic renal and hepatic disorders or calcific aortas. Many investigators have compared the cohorts of patients undergoing coronary revascularization with and without the aid of cardiopulmonary bypass and reported higher enzymatic increases implying myocardial injury in cardiopulmonary bypass group. The recent introduction of sophisticated stabilizing devices and exposure technique has resulted in an increased graft patency.[18] Therefore, OPCAB surgery has been used as an alternative approach for all coronary territories and for as many anastomosis as needed. As OPCAB surgery is performed while the heart beats, the O_2 consumption of the myocardium was the main determinant of myocardial injury occurring during anastomosis. To decrease the myocardial ischemia-reperfusion injury, the degree and the duration of ischemia should be reduced. Therefore, control of the contractility of myocardium and heart rate are important for minimization of myocardial injury. This is also desired in OPCAB surgery for easing operative techniques. Intravenous short-acting beta- blocker usage is one of the most effective strategies to achieve this goal. Since the original description of the measurement of cardiac troponin T (cTnT) by Katus et al[19] in 1989 and subsequently of cardiac troponin I (cTnI)[19,20] there has been a revolution in the technology for cardiac marker measurement. Cardiac troponin T and I are cardiac-specific contractile proteins and are not found elsewhere in the body. Preoperatively troponin I and troponin T concentrations were undetectable in blood. Following operation, a steady rise was observed peaking at 24 hours but never reached significant levels implying serious myocardial injury. In a recent trial Krejca et al[21] stated that although the rates of perioperative mortality and morbidity were comparable in off-pump and on-pump groups, cTnT levels were obviously less in off-pump group. Koh et al[22] stated in a trial of 18 cases that cTnT levels have increased up to 0.13 (0.1-0.16) ng/ml in off-pump patients whereas in on-pump patients cTnT levels had an increase of up to 6.8 ng/ml (2.6-10.2 ng/ml). Wan et al[23] compared 26 on-pump and 18 off-pump patients and stated that cTnI levels were high in on-pump group. He reported that maximal cTnI levels were achieved at the 24th hour. Shiga et al[24] investigated 23 off-pump patients and has seen in 91.7 % of them an increase in cTnT levels. He reported that in 17.4% of cases followed-up with continuous ECG monitoring during operation disclosed transient ST segment elevation that were abolished as the occlusion was ceased. In our trial maximal levels of cTnT were encountered at the 24th hour (mean=0.152±0.06 maximal=0.37 ng/ml), which were consistent with the literature. Several studies had been reported in the literature that showed the differences between OPCAB and CCABG regarding myocardial injury occurring during operation. However, the effect of intraoperative factors that contributes to myocardial ischemic injury during OPCAB surgery had not been clearly identified. There was a recent study reported in 2005 that determined the effect of intra-operative factors on postoperative cTnT release during OPCAB surgery. Although this study was retrospective in nature and included a limited number of 22 patients, the results were interesting.[25] They reported that double product (product of heart rate and blood pressure) during anastomosis was the main determinant of cTnT release after OPCAB surgery. Besides, they also reported that

anastomosis time had no significant effect on cTnT release during surgery. Therefore, they stated that anastomotic precision rather than speed should always preferred in OPCAB surgery.

Our study clearly demonstrated that both the degree and duration of ischemia occurring during anastomosis of coronary artery affect the myocardial injury occurring during OPCAB surgery. Therefore, management of heart rate and myocardial contractility was desirable not only for precise anastomosis but also for myocardial protection during OPCAB surgery. Minimization of myocardial injury can be achieved by using intracoronary shunt and controlling of blood pressure and heart rate during occlusion period which are the main determinant of myocardial O2 consumption/ min. Besides, anastomosis should be finished as soon as possible and a short-acting beta-blocker is useful to decrease the myocardial injury.

There were several study limitations. Ours was a retrospective analysis of risk factors for intraoperative myocardial injury in a relatively small number of patients undergoing coronary revascularization. Data on larger study populations must be collected and mid and long-term outcomes must be analyzed. In addition, it remains unclear whether the improved myocardial performance associated with off-pump CABG surgery translates into clinically significant benefits reflected in improvement of the quality of life of these patients.

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