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# Surgery for Coronary Artery Disease

## Five-Year Follow-Up of a Randomized Comparison Between Off-Pump and On-Pump Stable Multivessel Coronary Artery Bypass Grafting. The MASS III Trial

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**Background**—Coronary artery bypass graft surgery with cardiopulmonary bypass is a safe, routine procedure. Nevertheless, significant morbidity remains, mostly because of the body's response to the nonphysiological nature of cardiopulmonary bypass. Few data are available on the effects of off-pump coronary artery bypass graft surgery (OPCAB) on cardiac events and long-term clinical outcomes.

**Methods and Results**—In a single-center randomized trial, 308 patients undergoing coronary artery bypass graft surgery were randomly assigned: 155 to OPCAB and 153 to on-pump CAB (ONCAB). Primary composite end points were death, myocardial infarction, further revascularization (surgery or angioplasty), or stroke. After 5-year follow-up, the primary composite end point was not different between groups (hazard ratio 0.71, 95% CI 0.41 to 1.22;  $P=0.21$ ). A statistical difference was found between OPCAB and ONCAB groups in the duration of surgery ( $240\pm 65$  versus  $300\pm 87.5$  minutes;  $P<0.001$ ), in the length of ICU stay ( $19.5\pm 17.8$  versus  $43\pm 17.0$  hours;  $P<0.001$ ), time to extubation ( $4.6\pm 6.8$  versus  $9.3\pm 5.7$  hours;  $P<0.001$ ), hospital stay ( $6\pm 2$  versus  $9\pm 2$  days;  $P<0.001$ ), higher incidence of atrial fibrillation (35 versus 4% of patients;  $P<0.001$ ), and blood requirements (31 versus 61% of patients;  $P<0.001$ ), respectively. The number of grafts per patient was higher in the ONCAB than the OPCAB group (2.97 versus 2.49 grafts/patient;  $P<0.001$ ).

**Conclusions**—No difference was found between groups in the primary composite end point at 5-years follow-up. Although OPCAB surgery was related to a lower number of grafts and higher episodes of atrial fibrillation, it had no significant implications related to long-term outcomes.

**Clinical Trial Registration**—URL: <http://www.controlled-trials.com>. Unique identifier: ISRCTN66068876. (*Circulation*. 2010;122[suppl 1]:S48–S52.)

**Key Words:** cardiopulmonary bypass ■ coronary artery surgery ■ ischemic heart disease ■ coronary heart disease

Coronary artery bypass grafting with extracorporeal circulation (on-pump) is a safe, routine procedure with low mortality in select patients.<sup>1</sup> This procedure with cardiac arrest allows performance of coronary artery anastomosis in a steady, bloodless surgical field.<sup>2</sup> Nevertheless, significant morbidity remains mostly because of the whole-body response to the nonphysiologic nature of extracorporeal circulation, leading to a propagation of systemic inflammatory response syndrome, such as cytokines and complements.<sup>3,4</sup> In addition, the use of on-pump and cardiac arrest may result in myocardial dysfunction and in some patients myocardial stunning, blending diathesis, neurological deficits, tissue edema, and renal impairment.<sup>5–7</sup> Furthermore, the on-pump method is associated with significant cerebral morbidity, usually manifested as cognitive decline or a stroke.<sup>8</sup> Recently, several studies have demonstrated that coronary artery bypass grafting can be carried out without extracorporeal circulation on a beating heart (off-pump).<sup>9,10</sup> Evidence

from previous studies indicates that in select patients undergoing off-pump surgery, there is better ventricular contraction preservation and mitochondrial function than with cardiac arrest.<sup>11,12</sup> Avoidance of the off-pump method may thus confer the potential advantage of minimizing the risks of overall damage. Nevertheless, few data are available on the effects of off-pump surgery on myocardial function and long-term clinical outcome as part of a randomized study in elective patients. We undertook a prospective, randomized, controlled trial to compare patients with multivessel coronary artery disease, stable angina, and preserved ventricular function, undergoing coronary artery bypass grafting with and without extracorporeal circulation.

### Methods

#### Study Design and Patients

Details of The MASS III design, study protocol, patient selection, and inclusion criteria, have been reported previously.<sup>13</sup> Briefly,

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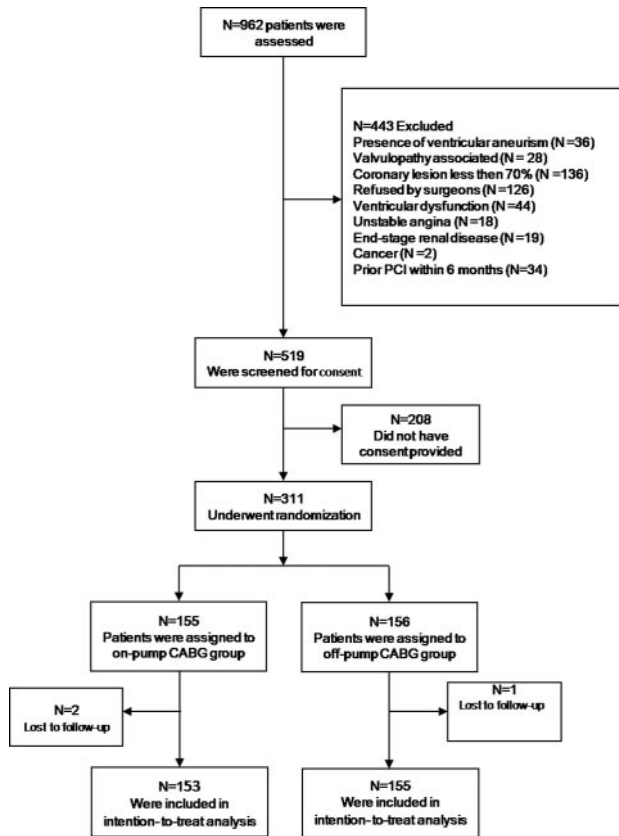
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**Figure 1.** Number of patients assessed, enrolled, and randomized in the trial.

patients with angiographically documented proximal multivessel coronary stenosis of  $>70\%$  by visual assessment, stable angina, and preserved ventricular function were considered for inclusion. Patients were enrolled and randomized if the surgeons agreed that revascularization could be attained by either strategy. All angiograms were reviewed, and a surgical plan was documented before randomization. Patients were eligible if they were referred for isolated coronary bypass surgery for the first time and an off-pump procedure was deemed technically feasible. Patients were excluded if they required emergency or concomitant major surgery, unstable angina requiring emergency revascularization, ventricular aneurysm requiring repair, and end left ventricular ejection fraction of  $<40\%$ . Patients were also excluded if they were unable to provide written informed consent. The study was carried out according to the principles of the Declaration of Helsinki. The ethics committee of our institution approved the study protocol. All subjects gave informed consent. In Figure 1, we provide a diagram detailing all patients screened for the trial.

### Surgical and Anesthetic Techniques

Trial operators were required to perform optimum coronary revascularization in accordance with current best practices. The procedure was performed by surgeons experienced in both on-pump and off-pump bypass surgery. On-pump surgery used cardiopulmonary bypass in combination with cold crystalloid cardioplegia for myocardial protection. Off-pump surgery used the Octopus stabilizer (Medtronic, Inc) described in detail elsewhere.<sup>14</sup> In brief, the distal ends of the 2 suction arms of the stabilizer are placed on the beating heart on both sides of the target coronary artery. The proximal parts are fixed to the operating table. Through the application of negative pressure, the target area of the heart is sufficiently immobilized to allow the safe construction of the anastomosis of the graft with the recipient artery.

A standardized anesthetic protocol was used throughout the study. Cardiopulmonary bypass was established in a standardized manner,

with the use of a membrane oxygenator and a roller pump and without the use of cardiomy suction. The heart was exposed through a median-sternotomy incision. During on-pump surgery, patients were cooled to  $32^{\circ}\text{C}$ , whereas during off-pump surgery, patients were actively warmed to maintain a core temperature not lower than  $35^{\circ}\text{C}$ . Cold-blood cardioplegia was accomplished with antegrade delivery through the aortic root and retrograde delivery through the coronary sinus. A heparinization protocol of 300 U/kg for on-pump surgery and half-dose heparin for off-pump surgery was followed. Protamine was used to reverse the effects of heparinization only in the on-pump patients. All anastomoses were sutured by hand. In the off-pump patients, intracoronary shunts were not used routinely; indications for use included poor visibility, ST-segment changes, and homodynamic instability.

### Primary End Points

The primary composite end point was freedom from overall mortality, stroke, myocardial infarction, and additional revascularization. Stroke was defined as a focal brain injury that persisted for  $>24$  hours, combined with an increase in disability of at least 1 grade on the Ranking scale.<sup>15</sup> Myocardial infarction within 7 days from the coronary artery bypass grafting procedure was considered if elevation of CK-MB 5 times or more the upper limit of normal ( $>30$  ng/mL) or troponin I values  $>5$  ng/mL associated or not with the appearance of new pathological Q. The ECG criteria for new-Q-wave myocardial infarction was: new QS in 2 associated leads in the absence of left bundle-branch block (LBBB) Wolf-Parkinson white syndrome; or new QS in 2 associated leads, defined as  $\geq 0.04$  seconds broad and/or Q/R ratio  $\geq 1/4$ .<sup>16</sup> Secondary end points were freedom from angina and exercise-induced ischemia. Stable angina was defined according to the Canadian Cardiovascular Society classification.<sup>17</sup>

### Follow-Up

Adverse and other clinical events were tracked from randomization. Patients were assessed with follow-up visits every 6 months at the Heart Institute. Furthermore, unless contraindicated, patients underwent exercise induced-ischemia according to a modified Bruce protocol every year until of the end of study.

### Statistical Analysis

All data were analyzed on an intention-to-treat principle beginning immediately after randomization. The risk of an event after on-pump surgery was compared with that after off-pump surgery, and the results are presented as the absolute difference with the corresponding 95% CIs. Values are expressed as mean ( $\pm$ SD) or median (interquartile range, 25 to 75%) as appropriate. Dichotomous data were compared by the  $\chi^2$  statistic or Fisher exact test. Continuous variables that were not distributed normally, as evaluated through the Kolmogorov–Smirnov test, were compared by the Mann–Whitney test. Continuous variables with a normal distribution were compared by the Student's *t* test. All reported probability values are 2-sided. Event-free survival was graphically compared by using Kaplan–Meier curves. Cox regression was used to compare survival time with combined primary end points. A probability value of  $P < 0.05$  was considered statistically significant. These analyses were performed with SPSS, version 13.0 (SPSS, Inc). At the time the study was designed, we calculated that 153 patients in each group would provide 80% power to distinguish between 5-year event-free rates of 85 and 95% in the 2 groups.

## Results

### Patient Population

Between March 2001 and March 2006, 308 patients underwent randomization: 153 to on-pump surgery and 155 to off-pump surgery (Figure 1). Most baseline characteristics were similar in the 2 groups and are summarized in Table 1. The mean age was 60.4 in the on-pump patients and 61.4 in the off-pump group. The distribution of patients in Canadian Cardiovascular Society classes was similar in the 2 groups.

**Table 1. Baseline Characteristics Demographic and Clinical Profile**

Characteristics	Off-Pump (n=155)	On-Pump (n=153)
<b>Demographic profile</b>		
Age (yrs)	61	59
Age $\geq$ 65 years (%)	40	39
Male sex (%)	78	80
Current or past smokers (%)	57	58
<b>Medical history</b>		
Previous MI (%)	34	32
Hypertension (%)	34	37
Diabetes mellitus (%)	29	27
Angina CCS class II or III (%)	35	33
<b>Laboratory values (mg/dL)</b>		
Total cholesterol	224 $\pm$ 6	226 $\pm$ 4
LDL cholesterol	140 $\pm$ 12	138 $\pm$ 14
HDL cholesterol (median $\pm$ IQR)	39 $\pm$ 9	38 $\pm$ 8
Triglycerides (median $\pm$ IQR)	160 $\pm$ 90	164 $\pm$ 87
Glucose (median $\pm$ IQR)	105 $\pm$ 33	101 $\pm$ 35
Positive treadmill test (%)	82	80
<b>Angiographic findings</b>		
Two-vessel disease (%)	26	24
Three-vessel disease (%)	74	76
Mean ejection fraction (median $\pm$ IQR)	70 (10)	68 (10)

CCS, Canadian Cardiovascular Society; MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range.

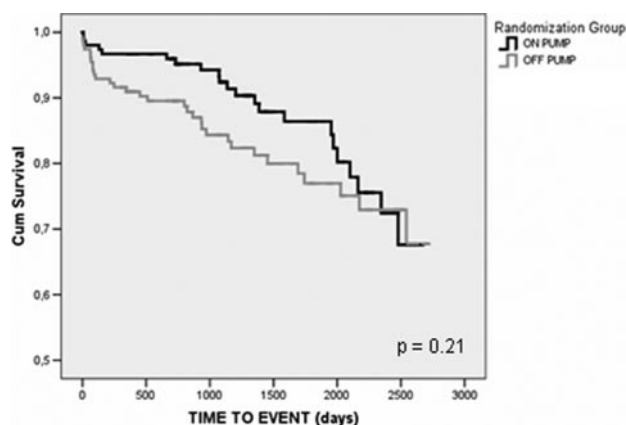
Twenty-eight percent had diabetes, and 33% had a myocardial infarction. Three patients who were randomly assigned to off-pump surgery were switched intraoperatively to on-pump surgery owing to hemodynamic instability. There was no significant difference in the quality of the native vessels between the 2 groups.

### Primary End Points

No significant differences occurred in major in-hospital complications between groups. No hospital mortalities occurred in the on-pump and off-pump patients. The same results were observed in relation to myocardial infarction and the need for in-hospital reoperation. During 5-year follow-up, no significant differences occurred between the groups with regards to the rates of event-free survival, namely the combined incidence of overall mortality, stroke, myocardial infarction, and additional revascularization (hazard ratio 0.71, 95% CI 0.41 to 1.22;  $P=0.21$ ) (Figure 2). The incidence of the primary and secondary end points for the 2 groups during the follow-up is shown in Table 2.

### Operative Data

The operative data are given in Table 3. The operation time was significantly shorter ( $P<0.001$ ) in the off-pump patients than in the on-pump group (240 $\pm$ 65 versus 300 $\pm$ 87.5 minutes). The number of grafts per patient was higher in the on-pump CAB (ONCAB) than the off-pump coronary artery bypass graft surgery group (2.97 versus 2.49 grafts per patient) was statistically different between the 2 groups ( $P<0.001$ ). However, the number of internal mammary artery anastomoses performed per patient (141 [91%] for off-pump



**Figure 2.** Probability of survival free of cardiac mortality, unstable angina requiring revascularization, and myocardial infarction among patients of the treatment groups.

and 142 [89%] for on-pump) was similar between groups. Arterial grafts were used in 91% of the total grafts in the off-pump patients and 89% in the on-pump group. There were no deaths in the on-pump group and 1 death in the off-pump group. The incidence of postoperative complications, such as infection, stroke, bleeding, and perioperative myocardial infarction, were also similar. The frequency of atrial fibrillation (AF) was higher in the off-pump than in the on-pump group (35 versus 4%,  $P<0.001$ ). On the other hand, the frequency of blood transfusion was lower in the off-pump group (31 versus 61%,  $P<0.001$ ) as shown in Table 4. The maximum CK-MB levels were higher in the on-pump group (Table 5).

### Secondary End Points

No significant differences existed between groups relating to the frequency of symptoms of angina and exercise-induced ischemia.

### Discussion

At in-hospital and 5-year follow-up, we found no statistically significant difference in cardiac outcomes or the incidence of the composite end point between patients with multi-vessel

**Table 2. Five-Year Outcomes**

Variables	Off-Pump (n=155)	On-Pump (n=153)	<i>P</i>
<b>Primary end-points</b>			
AMI [n] (%)	[10] (6.5)	[3] (1.9)	0.05
Stroke [n] (%)	[3] (1.9)	[5] (3.2)	0.50
Death [n] (%)	[13] (8.4)	[8] (5.2)	0.18
Further revascularization [n] (%)	[10] (6.5)	[9] (5.9)	0.84
<b>Secondary end-points</b>			
Angina CCS class II or III (%)	11.8	6.7	0.09
Positive treadmill test (%)	10.1	13.7	0.52

AMI, acute myocardial infarction; CCS, Canadian Cardiovascular Society; LITA, left internal mammary artery; RITA, right internal mammary artery; RADIAL, radial artery; GEA, gastroepiploic artery; LAD, left descending artery; LCX, left circumflex artery; RCA, right coronary artery; IQR, interquartile range; CPB, cardiopulmonary bypass; NA, not applicable.

*P* values as for 2-sided Pearson  $\chi^2$  test or Fisher exact test.



**Table 3. Perioperative Data**

Variables	Off-Pump (n=155)	On-Pump (n=153)	P
No. of distal anastomoses/ patient	2.60	3.18	<0.001
No. of grafts/patient	2.49	2.97	<0.001
Graft material no. (%)			
LITA	152 (98)	143 (94)	0.05
RITA	31 (20)	46 (30)	0.05
RADIAL	26 (17)	27 (18)	0.88
GEA	9 (6)	6 (4)	0.60
Vein grafts	116 (75)	123 (80)	0.30
Sequential Grafts	26 (17)	29 (19)	0.35
Territory grafted (%)			
LAD territory	149 (96)	150 (98)	0.50
LCX territory	102 (66)	125 (82)	0.002
RCA territory	118 (76)	121 (79)	0.59
Time in operating room (min) (median±IQR)	240±65	300±87.5	<0.001
Time on CPB (min) (median±IQR)	NA	80±31	...
Switch to CPB (n)	3	NA	...
Time in ICU (h) (median±IQR)	19.5±17.8	43±17.0	<0.001
Time to extubation (h) (median±IQR)	4.6±6.8	9.3±5.7	<0.001

disease and preserved ventricular function who underwent on-pump and those who underwent off-pump surgery.

Our study has potential limitations. Firstly, one should acknowledge the fact that it may be underpowered, because sample size calculations were derived from estimates of a larger treatment effect. In addition, it is a single-center study and has the bias inherent to these study designs, especially in a clinical scenario, where surgeons' experience is of paramount importance to the final clinical result. Finally, the limited sample size may preclude more thorough exploratory subgroup analysis aiming at identifying specific subgroup of patients where one treatment option is particularly better. Nevertheless, our results are similar to those described in recent meta-analysis of randomized trials that have suggested that off-pump is as safe and effective as on-pump technique.<sup>18-20</sup>

**Table 4. Perioperative and Hospital Complications**

Variables	Off-Pump (n=155)	On-Pump (n=153)	P
Intraoperative complications [n] (%)			
Ventricular arrhythmia	[3] (1.9)	[4] (2.6)	0.72
Bleeding	[5] (3.2)	[6] (3.9)	0.77
Hemodynamic instability	[6] (3.9)	[5] (3.3)	>0.99
IAPB support	[1] (0.6)	[1] (0.7)	>0.99
Operative death	[1] (0.6)	0	...
Inotropic requirements	[14] (9.0)	[16] (10.5)	0.70
Blood requirements	[48] (31)	[94] (61)	<0.001
Atrial fibrillation	[54] (35)	[6] (4)	<0.001
Wound infection	[3] (1.9)	[2] (1.3)	>0.99
Deep sternal infection	[2] (1.3)	[2] (1.3)	>0.99
Hemodialysis	[1] (0.6)	[1] (0.7)	>0.99
Myocardial infarction	[8] (5.2)	[16] (11)	0.09
Stroke	[2] (1.3)	[4] (2.6)	0.45

IAPB indicates intra-aortic balloon pump.

**Table 5. Postoperative Data**

Variables	Off-Pump (n=155)	On-Pump (n=153)	P
Time to discharge days (median±IQR)	6±2	9±2	<0.001
Maximum CK-MB, IU/L (median±IQR)	14.4±17.6	28.0±34.5	<0.001
Maximum serum creatinine mg/dL (median±IQR)	1.0±0.2	1.1±0.3	0.08

IQR indicates interquartile range; CK-MB, creatine kinase isoenzyme MB.

Interestingly, however, in a recent publication, Shoryer et al<sup>21</sup> showed, in the Veterans Affairs Randomized On/Off Bypass (ROOBY) Study, a higher composite outcomes incidence in the off-pump group at 1-year follow-up. In comparing these results with ours, one should highlight the shorter follow-up time and the rather variable experience of surgeons in performing off-pump procedures in the ROOBY study (more the 50% of surgeries in this study had residents as primary surgeons). On the other hand, it should remain in focus the relative reduced statistical power of our main end-point analysis.

In fact, in this complex scenario, multiple variables may be operant in defining the best strategy in a particular clinical context, and these deserve specific comments.

Despite the less invasive technique used, the incidence of postoperative AF was higher in off-pump patients in our study. The theoretical reasons for off-pump-related mechanisms of AF have been reported elsewhere.<sup>22</sup> In this study, the incidence of postoperative AF was higher (30% absolute difference) after off-pump surgery. It has been suggested that possible left atrial stretching with heart dislocation during revascularization of the lateral wall could lead to a higher risk of postoperative AF. In our study, on the other hand, the lower incidence of AF in the on-pump patients could be due to the routine administration of corticosteroid in all patients undergoing on-pump surgery in our service. This routine is based on the simple dosing regimen of corticosteroids that might have reduced the occurrence of frequent inflammatory processes after traumatic myopericarditis.

The off-pump strategy resulted in shorter intensive care unit and hospital stays, reduced use of blood products, shorter time in the operating room, and also shorter time to extubation.

Like the ROOBY study, completeness of revascularization was not similar between the 2 groups in our study. This condition may be related to the relative increase in the long-term incidence of acute myocardial infarction in off-pump patients, the group having a lower prevalence on complete revascularization. It is important to consider that 75% of patients had advanced coronary artery disease or a higher preoperative risk. The majority of patients who underwent coronary surgery had 3-vessel disease, and 25% 2-vessel disease. Moreover, these results did not affect the final outcome in terms of primary end points. In addition, the stable angina and preserved ventricular function in all patients contributed to a good prognosis for both strategies.

The cost of hospitalization for the 2 groups revealed that off-pump surgery needed more resources compared with on-pump. The use of the Octopus stabilizer and the need to keep the cardiopulmonary bypass with the staff members in stand-by may have contributed to the increased use of resources.<sup>23</sup> Moreover,

unlike at other centers, the stabilizer was used only once at the caution of health authorities. Indeed, a recently reported study concluded that off-pump is not associated with decreased cost.<sup>24</sup> On the other hand, indirect costs should be considered. In particular, our data showed notable reductions in blood products administered, time to discharge, time in the operating room, time in the ICU, and time to extubation; consequently, their complications and the overall costs of hospitalization might have been reduced.<sup>25</sup> Moreover, the shorter stay of the off-pump patients in the hospital allows the performance of an increased number of surgeries during the same time period. This social benefit must also be considered.

The magnitude of the benefit with off-pump surgery may depend on the clinical status of patients, and the majority of studies have been carried out on low-risk surgical patients. Claims of increased benefit in elderly and high-risk patients have now been studied, and many trials have suggested a reduction in mortality with off-pump surgery.<sup>26</sup> In the context of aging and ailing patients, this has several implications and might usher in a new pattern for off-pump surgery, with consideration of indications and contraindications.

The absence of recognized guidelines has meant that decisions on the use of extracorporeal circulation have been left to individual surgeons, many of whom remain reluctant to adopt the off-pump strategy. As some have argued, this cautious approach is justified, because a technically more demanding procedure is being offered in place of a successful, well-studied, and reproducible operation. However, if further evidence of the benefits of off-pump surgery is conclusive, this would have several implications for the future of cardiac surgery with regards to the quality of patient care and economic considerations.

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### Disclosures

None.

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