Prophylactic Application of an Intra-Aortic Balloon Pump in High-Risk Patients Undergoing Off-Pump Coronary Artery Bypass Grafting

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Key Words
High-risk patients · Intra-aortic balloon pump · Low cardiac output · Off-pump coronary artery bypass grafting · Prophylactic therapy

Abstract
Background: An intra-aortic balloon pump (IABP) is the most commonly used circulatory assist device in cardiac surgery. We hypothesized that prophylactic application of an IABP improves early clinical outcome of high-risk patients undergoing scheduled off-pump coronary artery bypass grafting (OPCABG).

Methods: From January 2010 to December 2013, hemodynamically stable, high-risk patients undergoing scheduled OPCABG with preincision use of an IABP were recruited to the IABP group. Using the propensity score-matching method, every patient in the IABP group was matched with another patient (the control group) with a similar propensity score who received an IABP on an as-needed basis during or after OPCABG. Surgical mortality and major morbidity rates were compared between groups.

Results: A total of 116 patient pairs were included in this study. In patients in the IABP group, postoperative low cardiac output and respiratory as well as renal failure were less frequent, intensive care unit stay was shorter, and surgical mortality was lower compared to patients in the control group. In multivariate logistic regression, timing of IABP implantation, as an independent risk factor, was associated with postoperative low cardiac output (OR = 2.02, 95% CI 1.28–5.76), respiratory failure (OR = 1.86, 95% CI 1.19–4.27), renal failure (OR = 2.96, 95% CI 1.51–6.63) and surgical mortality (OR = 2.45, 95% CI 1.42–6.07).

Conclusions: Prophylactic application of an IABP improves postoperative cardiac performance, reduces respiratory and renal complications, and consequently lowers surgical mortality in high-risk patients undergoing scheduled OPCABG.

Introduction
In 1962, an intra-aortic balloon pump (IABP), a device for mechanical circulatory support, was first applied in humans by Moulopoulos et al. [1]. Subsequently, Kantrowitz et al. [2] reported that 1 of 3 patients with cardiogenic shock due to myocardial infarction refractory to medical therapy survived after application of an IABP. At present, IABP has become the most commonly used device for cir-
culatory assistance in cardiac surgery, and approximately 70,000 IABP are inserted annually in the United States [3]. Timing of IABP implantation has been shown to be closely related to mortality: preoperative insertion is associated with a mortality of 18.8–19.6%; intra-operative insertion with 27.6–32.3%, and postoperative insertion with 39–40.5% [4]. Previous studies showed that prophylactic application of an IABP improved the early clinical outcome of high-risk patients undergoing bypass grafting [5, 6]. Nevertheless, several clinical studies reported that no survival advantage was found after prophylactic application of an IABP in hemodynamically stable, high-risk patients treated with bypass grafting compared to the application of a balloon pump on an as-needed basis during or after coronary artery bypass grafting (CABG) [7, 8].

Compared with on-pump CABG, off-pump CABG (OPCABG) may be helpful to reduce early mortality and morbidity rates in high-risk patients because it avoids the use of cardiopulmonary bypass and cardioplegic arrest [9]. However, in patients hemodynamic instability or ventricular fibrillation, OPCABG has to be urgently switched to on-pump CABG during surgery, which may result in severe myocardial injury and cause cardiac dysfunction, hence increasing the postoperative morbidity and mortality. Previous reports have shown that the mortality is about 32% following acute conversion of OPCABG to on-pump CABG [10]. IABP is helpful to support the failing heart and reduce the requirement for urgent switching to on-pump CABG during OPCABG [11].

Based on the above-mentioned findings, timing of the IABP application remains controversial [8]. In addition, previous studies did not focus on the evaluation of the timing of the IABP application in high-risk patients undergoing scheduled OPCABG. For this retrospective study, using the propensity score-matching method, we recruited 116 pairs of hemodynamically stable, high-risk patients scheduled for OPCABG who received pre-incision use of an IABP (IABP group) or an IABP procedure on an as-needed basis during or after OPCABG. Surgical mortality and major postoperative morbidity rates were compared between both groups in order to test the hypothesis that prophylactic application of an IABP improves the early clinical outcome in hemodynamically stable, high-risk patients undergoing scheduled OPCABG.

### Materials and Methods

#### Patients and Grouping

Hemodynamically stable, high-risk patients undergoing scheduled OPCABG were included in the study. Patients with an additive European system for cardiac operative risk evaluation (EuroSCORE) score of over 6 (the EuroSCORE score was determined prior to both IABP implantation and OPCABG) and meeting two or more of the following criteria were regarded as high-risk patients:

1. left-ventricular ejection fraction <40%;
2. left-ventricular end-diastolic internal diameter >65 mm;
3. left main stenosis >70%;
4. refractory unstable angina despite intravenous administration of heparin sodium and nitroglycerine, and
5. diffuse coronary artery disease (defined as the requirement for four or more distal anastomoses to achieve complete revascularization).

Exclusion criteria included IABP implantation prior to CABG for poorly controlled preoperative ventricular arrhythmias or mechanical complications (for example, ventricular septal perforation) due to acute myocardial infarction, emergent or urgent CABG surgery, and failed percutaneous transluminal coronary angioplasty within 6 h before CABG. Patients undergoing urgent switching from off-pump to on-pump CABG during surgery were also excluded.

All patients meeting the criteria mentioned above and with pre-incision use of an IABP were recruited from our center between January 2010 and December 2013 as IABP group. Using the propensity score-matching method, every patient in the IABP group was matched with another patient (control group) with a similar propensity score receiving an IABP implantation on an as needed basis during or after OPCABG in our center from January 2009 to December 2013.

#### IABP

In patients in the IABP group, a balloon pump was placed before OPCABG, whereas in patients in the control group IABP was implanted on an as-needed basis during or after OPCABG. After percutaneous puncture of the femoral artery, an 8-french balloon catheter (a 30- or 40-ml balloon pump depending on the patient’s height as well as weight; Arrow) was introduced with a guidewire through an arterial sheath and positioned. Then, the balloon catheter was connected to an AutoCAT Datascope pump (Datascope, Oakland, N.J., USA). Immediately after IABP implantation, chest X-ray examination was conducted to judge whether the position of the pump catheter was correct. Unless contraindicated, in all patients anticoagulant therapy with intravenous heparin was initiated as soon as the mediastinal drainage was below 50 ml/h after surgery, aiming to keep activated partial thromboplastin time at 1.5–2 times the normal value. Use of an IABP was discontinued when hemodynamic stability was restored (cardiac index of >2.0 l/min/m² with minimal inotropic support). Before IABP discontinuation, echocardiography was performed to evaluate left-ventricular ejection fraction and global and regional wall contractility.

#### OPCABG

In addition to the preoperative characteristics, the coronary anatomy of each patient was carefully evaluated for the assignment of off-pump or on-pump CABG. In every patient, complete anatomic revascularization of all lesioned vessels with a luminal diameter ≥1 mm was considered necessary. If a surgeon judged a complete revascularization feasible on the beating heart, OPCABG was completed. In patients in whom the location or the quality of target vessels and the preoperative characteristics (e.g. a large left ventricle) made the off-pump revascularization technically challenging, on-pump CABG was scheduled. In our center, OPCABG has...
been performed routinely for >5 years before study initiation, and all of the operations were performed by 3 surgeons with extensive experience in both off-pump and on-pump CABG (each surgeon performed at least 50% of their CABG procedures as OPCABG).

OPCABG is performed after a median sternotomy. Patients are intravenously anticoagulated with 1 mg/kg heparin to achieve an activated clotting time of >300 s. The central temperature, measured by a pulmonary artery catheter, was maintained at >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 x 70 cm) gauze swabs and a tissue stabilizer (Octopus; Medtronic Corporation, Minneapolis, Minn., USA). Body position changes and gravity support (Trendelenburg, right and left table rotations), in combination with administration of vasoactive agents, were carried out to stabilize the hemodynamics during surgery. A CO₂ blower/NaCl mister device was used in situations where a bloodless field was not achieved after proximal target vessel occlusion. An intracoronary shunt (Medtronic Corporation) was used during grafting. Blood lost was collected within a cell salvage device and reinfused before the completion of surgery. Grafting was always performed from the left internal mammary artery to the left anterior descending coronary artery, followed by grafting of the circumflex coronary artery and right coronary artery using a radial artery or a saphenous vein. Before the proximal anastomosis of grafts was performed, ascending aortic sclerosis or calcification was identified. The quality of the base and reviewed using a standard data collection form. Patients

Clinical End Points

The primary end point was surgical mortality, which was defined as death occurring during the hospitalization after surgery (within 30 days) or death occurring after discharge, but within 30 days after surgery, unless the cause of death was clearly unrelated to the surgery.

The secondary end point was major morbidity. The low cardiac output syndrome (LCS) was diagnosed according to the following criteria: (1) requirement for inotropic support with vasoactive drugs or mechanical circulatory support with IABP to maintain systolic blood pressure >90 mm Hg after correction of all electrolytes and blood gas abnormalities and adjustment of preload volume to its optimal value and (2) signs of improvement in body perfusion after correction of all electrolytes and blood gas abnormalities and adjustment of the preload volume to its optimal value. Postoperative acute myocardial infarction was defined by either the appearance of new Q waves in 2 or more contiguous leads on the electrocardiogram or an increase in the creatine kinase MB isoenzyme fraction of more than 50 U and of more than 7% of the total creatine kinase. After surgery, any episode of atrial fibrillation lasting >5 min with or without symptoms was defined as postoperative atrial fibrillation. Postoperative pneumonia was defined as a positive result in a sputum culture requiring anti-infective treatment or chest X-ray-diagnosed pneumonia following cardiac surgery. Reperfusion for bleeding was defined as reperfusion to control bleeding within 36 h following initial surgery. Postoperative respiratory failure was defined as mechanical ventilation continuing for more than 72 h or reintubation following cardiac surgery. Postoperative renal failure was defined as an increase in plasma creatinine of >2 associated with urine production <0.5 ml/kg/h for 12 h. Postoperative stroke was defined as a permanent neurologic deficit persisting either at discharge or until death. Wound infection was recognized on the basis of criteria developed by the US Centers for Disease Control and Prevention [12].

In addition, within 24 h after surgery, inotropes were quantitatively evaluated by the inotropic score according to the following formula: [(dopamine + dobutamine) x 1] + (milrinone x 15) + (epinephrine + norepinephrine + isoprenaline) x 100 [13]. The duration of mechanical ventilation and IABP support and the length of stay in the intensive care unit were also recorded.

Blood Sampling and Biochemical Analysis

From each patient, 2 ml of venous blood were collected preoperatively, on the day of IABP implantation, and then 1, 2, 3 and 5 days after IABP implantation for the detection of cardiac troponin I (cTnI), respectively. Blood samples were transferred into dry tubes and stored at 4°C until centrifugation. Plasma was separated after centrifugation and stored at –80°C for the detection of cTnI using the cTnI kit (Beckman Coulter Inc., Chaska, Minn., USA). Data were expressed as nanograms per milliliter (normal reference value in our hospital: <0.15 ng/ml). The cTnI concentration was measured by individuals blinded to this study.

Statistical Analysis

Perioperative data were obtained from our institutional database and reviewed using a standard data collection form. Patients were regularly followed up for at least 3 months after discharge. This study protocol was approved by the Ethics Committee of the Fudan University and is in accordance to the Declaration of Helsinki.

Categorical variables are presented as frequencies and percentages, and continuous variables as means ± SD. Continuous variables were compared using Student’s t test, and categorical variables with the χ² test and Fisher’s exact test, where appropriate. Stepwise multivariate logistic regression was also conducted to assess the impact of the timing of IABP implantation (placing an IABP on an as-needed basis during or after OPCABG versus preincision use of an IABP) as an independent variable on the surgical mortality and major morbidity. A value of two-sided p < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS software (version 17.0; SPSS Inc., Chicago, Ill., USA).

Results

Study Population

From January 2010 to December 2013, a total of 126 consecutive, hemodynamically stable, high-risk patients undergoing scheduled OPCABG who received preincision use of an IABP in our center were included into the IABP group. Ten patients were excluded (urgent switching from off-pump to on-pump CABG during surgery in 4 patients, IABP implantation prior to surgery for hemo-

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Cardiology 2015:131:109–115
DOI: 10.1159/000377720
dynamic instability due to mechanical complications following acute myocardial infarction in 4 patients and IABP implantation prior to surgery for poorly controlled preoperative ventricular arrhythmias due to acute myocardial infarction in 2 patients); finally, in the IABP group, the data of 116 patients were analyzed. Using the propensity score-matching method, every patient in the IABP group was matched with another patient (control group) with a similar propensity score who received a balloon pump on an as-needed basis during or after OPCABG in our center from January 2009 to December 2013.

The pre- and intraoperative clinical data are listed in table 1. There were no significant differences in age, gender, body mass index, recent smoking, comorbidities, cardiac function and severity of coronary artery disease between both groups. The number of bypass conduits ranged from 2 to 5 (mean: 3.4 ± 0.9) in the IABP group and in the control group (mean: 3.2 ± 0.8; nonsignificant difference).

Clinical Outcomes
Postoperative results are shown in table 2. Compared with patients in the control group, patients in the IABP group had a significantly shorter duration of IABP support (3.8 ± 1.5 vs. 5.2 ± 1.9 days, p < 0.0001), shorter duration of inotropic drug treatment (4.2 ± 1.9 vs. 6.5 ± 2.7 days, p < 0.0001), shorter duration of mechanical ventilation (2.1 ± 1.2 vs. 3.3 ± 1.7 days, p < 0.0001) as well as lower surgical mortality (6.0 vs. 16.4%, p = 0.0206).

In stepwise multivariate logistic regression analysis (table 3), the timing of IABP implantation (placing an IABP on an as-needed basis during or after OPCABG vs. preincision use of an IABP) as an independent risk factor...
significantly affected postoperative LCOS (OR = 2.02, 95% CI 1.28–5.76, p = 0.0112), postoperative respiratory failure (OR = 1.86, 95% CI 1.19–4.27, p = 0.0306), postoperative renal failure (OR = 2.96, 95% CI 1.51–6.63, p = 0.0037) and surgical mortality (OR = 2.45, 95% CI 1.42–6.07, p = 0.0052).

A total of 26 patients died; surgical mortality amounted to 11.2%. The causes of death were as follows: postoperative LCOS (n = 13), sepsis (n = 8), malignant arrhythmia (n = 3) and gastrointestinal bleeding (n = 2).

In addition, 92.6% patients (101/109) in the IABP group and 93.8% (91/97) in the control group were followed up for at least 3 months. No death or repeat revascularization was observed in the follow-up period.

**Plasma cTnI**

The plasma cTnI at the different time points is shown in figure 1. Serum plasma cTnI increased significantly on the day of IABP implantation, followed by a slow decline in both groups (time effect, F = 45.25, p = 0.000 for the IABP group, and F = 246.64, p = 0.000 for the control group). Baseline plasma cTnI was similar between both groups. Significant differences in plasma cTnI levels between the groups were found on the day of IABP implantation and on days 1, 2, 3 and 5 after IABP implantation (15.81 ± 4.13 vs. 3.89 ± 0.67 ng/ml, p < 0.0001; 13.91 ± 3.12 vs. 2.98 ± 0.63 ng/ml, p < 0.0001; 10.23 ± 2.15 vs. 2.12 ± 0.37 ng/ml, p < 0.0001; 6.19 ± 0.85 vs. 1.68 ± 0.31 ng/ml, p < 0.0001, and 3.35 ± 0.69 vs. 0.81 ± 0.13 ng/ml, p = 0.0002).

**IABP-Related Complications**

Overall, 8 patients (3.4%) developed either limb ischemia or hematoma at the site of IABP insertion. One patient received amputation due to serious limb ischemia, and the remaining 7 patients recovered after discontinuation of IABP. There was no IABP-related mortality.

**Discussion**

IABP, the most commonly used device for mechanical circulatory support, has been proven to improve LCOS and left-ventricular failure following CABG via reducing the left-ventricular afterload and myocardial oxygen consumption, improving the subendocardial perfusion and promoting the redistribution of coronary blood flow to the ischemic myocardium [8, 14–17]. In addition, IABP helps to improve the hemodynamic stability and reduce the myocardial oxygen consumption when the heart is displaced to expose and then graft the target coronary artery during OPCABG, especially in high-risk patients [11]. Previously, IABP, a rescue therapy in case of failure of pharmacotherapy to improve LCOS following CABG, was found to be associated with a high mortality (40–50%) and high rate of IABP-related complications due to prolonged IABP support [18]. Several clinical studies have shown that prophylactic application of an IABP resulted in reduced surgical mortality and postoperative morbidity in high-risk patients undergoing CABG surgery [19, 20]. Nevertheless, studies also reported that no survival advantage was found in the prophylactic application of an IABP in hemodynamically stable, high-risk patients undergoing bypass grafting, as opposed to the placement of an IABP on an as-needed basis during or after surgery [7, 8]. Although the practicability of an IABP has been extensively investigated in the past 3 decades, the timing of application of an IABP remained uncertain in high-risk patients undergoing OPCABG [21, 22]. In this study, patients in the IABP group had significantly lower incidence rates of postoperative LCOS, and respiratory as well as renal failure compared to patients in the control group, which indicates that preincision use of an IABP helped to preserve the cardiopulmonary and renal function. A significant reduction in plasma cTnI in the IABP group compared to the control group might imply that myocardial injury in the IABP group was much lower than in the control group, suggesting that preincision use of an IABP helped to reduce myocardial injury compared to the IABP application on an as-needed basis during or after OPCABG. Less myocardial injury, better cardiopulmonary as well as renal protection, in association with a shorter treatment with inotropic drugs as well as a shorter duration of mechanical ventilation, may contribute to the reductions in the surgical mortality and postoperative morbidity as well as the accelerated recovery in hemodynamically stable, high-risk patients undergoing scheduled OPCABG with preincision use of an IABP.
In the IABP group, 7 of 116 patients (6.03%) died. In the control group, 2 of 19 patients (10.53%) with intraoperative emergency IABP implantation due to hypotension or arrhythmia died in the perioperative period, and 17 of 97 patients (17.53%) with emergency IABP implantation due to postoperative LCOS died in the postoperative period. Surgical mortality was signifi cantly lower in the IABP group compared to the control group (p = 0.0206). This may be ascribed to the severity of myocardial injury because patients receiving IABP implantation on an as-needed basis during or after OPCABG had more serious myocardial injury and thus severely impaired cardiac function, which was conﬁ rmed by the changes in plasma cTnI levels over time.

In this study, the timing of IABP implantation, as an independent risk factor, signiﬁ cantly aﬀ ected postoperative LCOS, postoperative respiratory failure, postoperative renal failure and surgical mortality. In a meta-analysis conducted by Field et al. [23], preoperative IABP in patients undergoing CABG showed a signiﬁ cant beneﬁ t with respect to the in-hospital mortality and postoperative cardiac index. A study by Etienne et al. [24] indicated that preoperative IABP support associated with OPCABG eﬀ ectively reduced in-hospital mortality compared with the Euro-SCORE-predicted mortality. Another meta-analysis of randomized controlled trials supported that prophylactic application of IABP in hemodynamically stable, high-risk CABG patients was helpful to reduce in-hospital mortality [8]. These results are in line with our ﬁ ndings about in-hospital mortality. Baskett et al. [25] found a higher in-hospital mortality after preoperative IABP, which was inconsistent with our results regarding clinical outcomes. This may be ascribed to the higher proportion of urgent operations in their series, whereas patients receiving emergent or urgent CABG surgery were excluded in our study. In addition, Holman et al. [7] reported that, except for shorter postoperative hospitalization, no survival advantage was found for the prophylactic application of IABP in hemodynamically stable, high-risk CABG patients compared to IABP placement on an as-needed basis during or after surgery. This was in line with our ﬁ nding about postoperative hospitalization but diﬀ erent from those about surgical mortality and postoperative morbidity. This may be explained by the type of operation, because this study only focused on OPCABG.

The incidence of IABP-related complications in our study was 3.4%, which was similar to that in other series [26]. There was no IABP-related death in our study. The careful and cautious percutaneous femoral artery catheterization, close monitoring of puncture limb skin temperature and puncture side dorsalis pedis artery pulse condition, standardized anticoagulation and discontinuation of IABP as early as possible were necessary to reduce or avoid these complications [27].

The present study has some limitations. It was a retrospective study. Although the propensity score was matched between both groups, unobserved confounders and selection bias between patients with prophylactic application of an IABP and those with IABP use on an as-needed basis during or after OPCABG cannot be eliminated. In addition, all the enrolled subjects were Chinese patients who underwent revascularization using the off-pump technique in a single center, which limits the generalization of our ﬁ ndings.

In summary, compared to the placement of an IABP on an as-needed basis during or after OPCABG, preincision use of an IABP improves the postoperative cardiac function, reduces respiratory and renal complications, and lowers the surgical mortality in hemodynamically stable, high-risk patients undergoing scheduled OPCABG.

Conflict of Interest

The authors declare that they have no conﬂ ict of interest.


