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Concomitant Off-Pump Coronary Artery Bypass Grafting Results in Improved In-Hospital Outcomes for Patients with Ischemic Mitral Regurgitation Undergoing Surgery

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ABSTRACT

Objective: Surgical management of ischemic mitral regurgitation (IMR) has primarily consisted of revascularization with or without the addition of mitral valve repair or replacement. We hypothesize that performing off-pump coronary artery bypass (OPCAB) grafting before fixing MR improves in-hospital outcomes for patients with IMR undergoing surgery.

Methods: From January 2000 through December 2010, a total of 96 consecutive patients with moderate or severe IMR, as determined by preoperative echocardiography, underwent on-pump coronary artery bypass grafting (CABG) (n = 66) or OPCAB (n = 30) revascularization with concomitant mitral valve repair or replacement. A retrospective analysis of a prospectively collected cardiac surgery database (PATS; Dendrite Clinical Systems, Oxford, UK) was performed. In addition, medical notes and charts were reviewed for all study patients.

Results: The 2 groups had similar preoperative demographic and EuroSCORE risk-stratification characteristics. The operative mortality rate for the entire cohort was 9.4%. Patients who underwent OPCAB grafting had a lower operative mortality than those who underwent CABG (3.3% versus 12.1%; $P = .006$). The mean ±SD cardiopulmonary bypass time (82.7 ± 34.7 minutes versus 160.7 ± 45.2 minutes; $P < .001$) and cross-clamp time (49.0 ± 22.4 minutes versus 103.4 ± 39.5 minutes; $P < .001$) were significantly shorter in the off-pump group than in the on-pump group. The OPCAB group also had significantly less in-hospital morbidity and shorter stays in the intensive care unit and the hospital.

Conclusion: Our analysis shows that OPCAB grafting (compared with conventional CABG) before repairing MR is associated with favorable in-hospital outcomes for patients undergoing surgery for IMR.

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INTRODUCTION

Surgical management of ischemic mitral regurgitation (IMR) remains a challenge, and the preferred surgical procedure remains controversial [Iung 2003; Vahanian 2007]. Surgery for IMR has consisted primarily of revascularization with or without the addition of mitral valve repair via a variety of techniques, including suture, band or ring annuloplasty, and mitral valve replacement [Anyanwu 2008]. The European Society of Cardiology guidelines recommend that patients with severe IMR (effective regurgitant orifice [ERO] area 20 mm^2) who undergo surgical myocardial revascularization should be treated with combined surgery (class I, level of evidence C) [Vahanian 2007]. On the other hand, patients with mild or trivial IMR should not undergo operation. The most controversial issue is the role of combined therapy for patients with moderate IMR (ERO >10 mm^2 but <20 mm^2). In the absence of clear evidence, management is usually individualized, with the choice of surgical procedure based on the presence of myocardial viability, inducible ischemia, and the dynamic component of MR [Piérard 2010]. It is intuitively apparent that patients with a dynamic increase in MR during exercise (exercise-induced increase in the ERO area 13 mm^2) could be candidates for combined surgery; however, such an approach has not yet been validated [Piérard 2010]. At the same time, the morbidity and mortality associated with combined mitral valve intervention and surgical myocardial revascularization are high, and long-term survival after this combination is quite poor [Hickey 1988; Rankin 1989].

In recent years, efforts have been directed toward reducing the morbidity and mortality associated with cardiac surgical interventions. Concerns regarding the morbidity associated with conventional coronary artery bypass grafting (CABG) on cardiopulmonary bypass (CPB) have led to a resurgence of interest in off-pump bypass surgery during the last decade, with the expectation that it would be safer if CPB could be avoided [Raja 2008]. Evidence from both a large number of randomized controlled trials and observational studies has validated the safety and efficacy of off-pump coronary artery bypass (OPCAB) grafting [Al-Ruzzeh 2006; Raja 2008; Puskas 2011]. Increasing evidence suggests that OPCAB disproportionately benefits high-risk patients [Puskas 2009; Lemma 2012]. Because patients with IMR are a high-risk category,

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we hypothesize that performing OPCAB grafting before fixing mitral regurgitation improves in-hospital outcomes for patients with IMR undergoing surgery.

Table 1. Preoperative Patient Characteristics*

Variable	CABG + MVR (n = 66)	OPCAB + MVR (n = 30)	*P*
Age, years	65.3 ± 12.2	66 ± 13.1	.79
Male sex, n	46 (69.7%)	20 (66.6%)	.42
Diabetes, n	36 (54.5%)	17 (56.6%)	.78
Hypertension, n	27 (40.9%)	14 (46.6%)	.52
Hypercholesterolemia, n	23 (34.8%)	11 (36.6%)	.78
Smoker, n†	15 (22.7%)	7 (23.3%)	.71
Previous PCI	6 (9.1%)	5 (16.6%)	.07
Previous MI, n			
Anterior	10 (15.2%)	5 (16.6%)	.87
Posterolateral	51 (77.3%)	23 (76.7%)	.81
Both	5 (7.5%)	2 (6.7%)	.83
COPD, n	6 (9.1%)	4 (13.3%)	.46
Renal insufficiency, n	5 (7.6%)	3 (10%)	.55
PVD, n	4 (6.1%)	2 (6.6%)	.91
CVA, n	3 (4.5%)	2 (6.6%)	.40
IABP, n	5 (7.6%)	6 (20%)	.02
Two-vessel disease, n	17 (25.8%)	8 (26.6%)	.87
Three-vessel disease, n	49 (74.2%)	22 (73.3%)	.84
LVEF, %	44 ± 8	43 ± 9	.71
MR severity, n			
Moderate	6 (9.1%)	3 (10%)	.83
Severe	60 (90.9%)	27 (90%)	.91
sPAP, mm Hg	42 ± 11	42 ± 9	.87
Urgent surgery, n	6 (9.1%)	5 (16.6%)	.07
Elective surgery, n	60 (90.9%)	25 (83.3%)	.84
Logistic EuroSCORE	6.5 ± 5.1	6.3 ± 4.8	.51

*Data presented as the mean ± SD or as a number (percentage) are indicated. CABG indicates coronary artery bypass grafting; MVR, mitral valve repair/replacement; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; sPAP, systolic pulmonary artery pressure.

†Including ex-smokers and current smokers.

MATERIALS AND METHODS

Study Sample

This study constituted a retrospective analysis of a prospectively collected cardiac surgery database (PATS; Dendrite Clinical Systems, Oxford, UK). Owing to its retrospective nature, the Institutional Ethics Committee waived informed consent for this study. The PATS database captures detailed information on a wide range of preoperative, intraoperative, and hospital postoperative variables (including complications and mortality) for all patients who underwent cardiac surgery in our institution. The database was collected and reported in accordance with the database criteria of the Society for Cardiothoracic Surgery in Great Britain and Ireland. In addition, we reviewed the medical notes and charts of all the study patients. From January 2000 through December 2010, a total of 96 consecutive patients with moderate or severe IMR, as determined by preoperative echocardiography evaluations, underwent on-pump CABG (n = 66) or OPCAB (n = 30) revascularization with concomitant mitral valve repair or replacement (MVR). The characteristics of the 2 groups of patients are summarized in Table 1. Indications for surgical intervention were determined at a weekly review by cardiologists, cardiac surgeons, and cardiac radiologists. Patients were placed on a specific waiting list according to the urgency of their procedure. Myocardial viability was assessed with either cardiac magnetic resonance imaging or positron emission tomography. All of the patients with IMR who underwent surgical myocardial revascularization with an intervention involving the mitral valve only were included. To minimize surgical variability, we excluded patients in cases involving additional surgical ventricular restoration.

Operative Technique

Five surgeons performed the 96 operations. All interventions were performed via a midline sternotomy. Left and right internal mammary arteries (IMA) were harvested as pedicled or skeletonized grafts with minimal trauma and in accordance with the surgeon's preference. The grafts were treated with papaverine solution before use. The great saphenous vein was harvested with an open or endoscopic technique.

Conventional CABG on CPB was performed at 34°C. CPB was instituted with bicaval cannulation and with an ascending aorta perfusion cannula. Standard bypass management included membrane oxygenators, arterial line filters, and a nonpulsatile flow of 2.4 L/min per m^2, with a mean arterial pressure >50 mm Hg. The myocardium was protected by using intermittent antegrade cold blood cardioplegia (4:1 ratio of blood to crystalloid). Anticoagulation was achieved with 300 U/kg heparin. If required, the heparin dose was supplemented to maintain the activated clotting time >480 seconds; heparin was reversed with protamine at the end of the procedure.

All patients underwent conventional multivessel CABG with various combinations of the left and/or right IMA and saphenous vein grafts. All distal anastomoses on CPB were performed during a single aortic cross-clamping before the mitral valve intervention. The proximal graft anastomoses to the aorta were performed with partial cross-clamping of the ascending aorta on CPB after release of the aortic cross-clamp and closure of the left atrium.

One surgeon (M.A.) performed the OPCAB grafting before the mitral valve intervention. The heart was stabilized with the Octopus 3 suction-irrigation tissue-stabilization system (Medtronic, Minneapolis, MN, USA). A deep pericardial retraction suture helped position the heart for grafting. Anticoagulation was achieved with 150 U/kg heparin. If required, the heparin dose was supplemented to maintain the activated clotting time at >250 seconds; heparin was reversed with protamine at the end of the procedure. Blood pressure was continually optimized during the procedure, and the mean arterial pressure was maintained at >50 mm Hg by repositioning the heart and by the use intravenous fluids, the selective use of vasoconstrictors, or both. All distal and proximal anastomoses were constructed off pump before the mitral valve intervention, which was performed with the patient on CPB, as instituted in the aforementioned manner. During the period of aortic cross-clamping, IMA flow was controlled with a bulldog vascular clamp.

The mitral valve was exposed in all patients via a longitudinal atriotomy along the Waterston groove. Mitral valve annuloplasty was performed with a Carpentier-Edwards Physio Ring (Edwards Lifesciences, Irvine, CA, USA). The size of the ring was determined after careful measurement of the height of the anterior leaflet and the intercommissural distance; we then downsized the ring by 2 sizes (eg, use of size 26 when measurements indicated size 30). Rings were inserted with deep U-shaped simple horizontal Ethibond 2-0 sutures (Ethicon, Somerville, NJ, USA). Mitral valve replacement was performed with a Carpentier-Edwards Perimount bioprosthetic valve (Edwards Lifesciences) by means of pledgetted interrupted Ethibond 2-0 sutures (Ethicon). Surgical data are summarized in Table 2. All patients underwent intraoperative transesophageal echocardiographic assessment of the left ventricle and valve function after repair. Mitral valve repair was considered successful if there was no or only trivial residual MR postoperatively.

Table 2. Intraoperative Data*

Variable	CABG + MVR (n = 66)	OPCAB + MVR (n = 30)	*P*
CPB time, min	160.7 ± 45.2	82.7 ± 34.7	<.001
Aortic cross-clamp time, min	103.4 ± 39.5	49.0 ± 22.4	<.001
IMA graft, n	59 (89.4%)	27 (90%)	.89
Grafts/patient, n	2.9 ± 0.5	2.8 ± 0.6	.83
MV repair, n	65 (98.5%)	30 (100%)	.85
MV replacement, n	1 (1.5%)	0	—

*Data presented as the mean ± SD or as a number (percentage) are indicated. CABG indicates coronary artery bypass grafting; MVR, mitral valve repair/replacement; OPCAB, off-pump coronary artery bypass; CPB, cardiopulmonary bypass; IMA, internal mammary artery; MV, mitral valve.

Postoperative Management

Postoperative intensive care unit (ICU) management was standardized for all patients. All patients received intravenous nitroglycerin infusions (0.1-8 μg/kg per minute) for the first 24 hours unless the patient was hypotensive (systolic blood pressure <90 mm Hg). The choice of inotropic agents was dictated by the hemodynamic data. Other routine medications included daily aspirin administration and the resumption of the use of cholesterol-lowering agents and β-blockers. Diuretics, angiotensin-converting enzyme inhibitors, and warfarin were gradually introduced when clinically indicated.

Variables and Data Collection

Preoperative variables of interest included age, sex, smoking history, chronic obstructive pulmonary disease, diabetes, hypercholesterolemia, renal insufficiency (preoperative serum creatinine 200 μmol/L), hypertension, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction (EF), urgency (operation performed <24 hours versus >24 hours from time of referral), previous myocardial infarction, prior percutaneous coronary interventions, number of diseased vessels, preoperative use of an intra-aortic balloon pump (IABP), logistic EuroSCORE, severity of MR, and systolic pulmonary artery pressure. Intraoperative variables of interest included CPB time, aortic cross-clamp time, number of distal anastomoses, and IMA use. Postoperative variables of interest included in-hospital mortality, postoperative IAB*P* use, stroke or transient ischemic attack, prolonged ventilation (>24 hours), atrial fibrillation, deep sternal infection, blood product use, hemofiltration, the use inotropes in patients leaving the operating room (OR), chest infection, return to the OR for bleeding, gastrointestinal complications, conversion to CPB, and lengths of stays in the ICU and hospital.

Statistical Analysis

Summary results for numeric variables were presented as the mean ± SD. Summary results for categorical variables were presented as the frequency and percentage. Group differences for numeric variables were evaluated with the Student t test or the Wilcoxon rank sum test, as appropriate. Group differences for categorical variables were evaluated with the χ^2 test or the Fisher exact test. A significance level of <.05 was used throughout. All analyses were performed with the SAS software package (release 9.1.3; SAS Institute, Cary, NC, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

RESULTS

The 2 groups had similar preoperative demographic and EuroSCORE risk-stratification characteristics (Table 1). Six patients (20%) in the OPCAB group had a preoperative prophylactic IABP, compared with 5 (7.6%) of the patients who underwent conventional CABG (P = .02). The 2 groups were not significantly different with respect to the intraoperative data, except for the CPB and aortic cross-clamp times. The total CPB times (82.7 ± 34.7 minutes versus 160.7 ± 45.2 minutes; P < .001) and cross-clamp times (49.0 ± 22.4 minutes versus 103.4 ± 39.5 minutes; P < .001) were significantly shorter in the off-pump group than in the on-pump group (Table 2).

The overall in-hospital mortality rate (<30 days) for the entire population was 9.4% (9 patients. One patient (3.3%)

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died in the group that underwent OPCAB plus MVR), and 8 patients (12.1%) died in the group that underwent CABG plus MVR (*P* = .01). Causes of in-hospital death were low cardiac output in 2 patients, ischemic bowel in 2 patients, and multiorgan failure in 5 patients.

Significantly more patients in the group that underwent CABG plus MVR required an IAB*P* postoperatively (*P* = .02), ventilation >24 hours (*P* = .04), more use of blood products (*P* = .01), and hemofiltration (*P* = .04), compared with the group that underwent OPCAB plus MVR. Similarly, significantly more patients in the group that underwent CABG plus MVR were returned to the OR for bleeding, chest infection, and pleural effusion(s) requiring intervention (Table 3). Finally, patients in the group that underwent CABG plus MVR had longer stays in the ICU (3.2 ± 1.0 days versus 2.1 ± 0.6 days; *P* = .03) and the hospital (13.3 ± 2.4 days versus 9.4 ± 1.2 days; *P* = .02).

Table 3. Postoperative Outcomes*

Variable	CABG + MVR (n = 66)	OPCAB + MVR (n = 30)	*P*
Patients with inotropes leaving OR, n	46 (69.6%)	12 (40%)	.02
Postoperative IABP, n	9 (13.6%)†	1 (3.3%)	.02
Atrial fibrillation, n	18 (27.2%)	9 (30%)	.68
Stroke/TIA, n	1/1 (3%)	1/0 (3.3%)	.91
Ventilation >24 h, n	12 (18.2%)	3 (10%)	.04
Deep sternal infection, n	2 (3%)	1 (3.3%)	.91
Blood product use, n	27 (40.9%)	7 (23.3%)	.01
Hemofiltration, n	14 (21.2%)	4 (13.3%)	.04
Return to OR for bleeding, n	6 (9.1%)	1 (3.3%)	.03
Chest infection, n	12 (18.2%)	3 (10%)	.04
Pleural effusion, n	7 (10.6%)	1 (3.3%)	.03
GI complications, n	3 (4.5%)	2 (6.6%)	.40
Conversion to CPB, n‡	0	1 (3.3%)	—
ICU stay, d	3.2 ± 1.0	2.1 ± 0.6	.03
Hospital stay, d	13.3 ± 2.4	9.4 ± 1.2	.02
In-hospital mortality, n	8 (12.1%)	1 (3.3%)	.01

*Data presented as the mean ± SD are indicated. CABG indicates coronary artery bypass grafting; MVR, mitral valve repair/replacement; OPCAB, off-pump coronary artery bypass; OR, operating room; IABP, intra-aortic balloon pump; TIA, transient ischemic attack; GI, gastrointestinal; CPB, cardiopulmonary bypass; ICU, intensive care unit.

†One patient had a left ventricular assist device.

‡Before completion of grafting.

DISCUSSION

IMR is a major source of patient morbidity and mortality. Although the frequency of IMR differs depends on the imaging modality used, estimates have indicated that nearly 20% to 30% of patients experience mitral valve insufficiency following a myocardial infarction [Grigioni 2001]. Furthermore, its intimate association with heart failure and poor outcomes for suboptimal medical management further complicates the management of clinically significant IMR. Recent evidence suggests that moderate or severe mitral regurgitation may be associated with a 3-fold increase in the adjusted risk of heart failure and a 1.6-fold increase in the risk-adjusted mortality at the 5-year follow-up [Bursi 2005]. In addition, unfavorable patient profiles and coexisting comorbid disease, including renal failure, chronic obstructive pulmonary disease, diabetes, and impaired left ventricular function [Gazoni 2007], further complicate the clinical picture for those with IMR. Consequently, surgical correction of this condition is often required.

Surgical operations for IMR include myocardial revascularization alone or mitral valve replacement or repair with concomitant myocardial revascularization [LaPar 2011]. Although myocardial revascularization alone may prove beneficial for some patients, a majority of the published series support the use of revascularization in combination with a mitral valve operation [Gillinov 2001; Grossi 2001; Micovic 2008]. Unfortunately, the combined approach is associated with significant mortality and morbidity [Hickey 1988; Rankin 1989; Gillinov 2001; Grossi 2001; Micovic 2008].

We hypothesized that altering the revascularization strategy from on pump to off pump could have a beneficial impact on the outcomes of surgery for IMR, and the results of our study have confirmed this hypothesis. Although the overall mortality rate (9.4%) for the entire cohort remains as high as previously reported [Gillinov 2001; Grossi 2001; Micovic 2008], the mortality rate for the patients who underwent OPCAB plus MVR was significantly lower (3.3%; *P* < .01). Furthermore, the majority of the postoperative outcomes were significantly better for this group. We believe that the most plausible explanation for these improved outcomes is the reduction in the aortic cross-clamp and total CPB times.

Abundant evidence suggests that despite the modern techniques of cardioprotection, the aortic cross-clamp time is an independent predictor of mortality and adverse outcomes in patients undergoing cardiac surgery [Doenst 2008; Healey 2009; Al-Sarrah 2011]. Similarly, prolonged CPB duration independently predicts postoperative morbidity and mortality after cardiac surgery [Salis 2008]. CPB is associated with an intense inflammatory response because of the conversion to laminar flow, blood contact with the artificial bypass surface, cold cardiac ischemia, and hypothermia [Larmann 2004]. This inflammatory response, which is characterized by the activation of 5 plasma protein systems and 5 types of blood cells, causes an acute, massive defense reaction that produces a consumptive coagulopathy; circulates >70 hormones, cytokines, chemokines, vasoactive substances, cytotoxins, reactive oxygen species, and proteases of the coagulation and fibrinolytic systems; induces mild to huge shifts in interstitial fluids; generates a host of microemboli (<500 μm); and causes temporary dysfunction of nearly every organ. More importantly, longer CPB and aortic cross-clamp times are associated with increases in the magnitude of this inflammatory response and with worse outcomes [Doenst 2008; Salis 2008; Al-Sarraf 2011].

Even though the CPB and aortic cross-clamp durations reported in this study are not excessively prolonged and almost similar to those reported in the literature for combining CABG with mitral valve intervention for IMR [Hickey 1988; Rankin 1989; Gillinov 2001; Grossi 2001; Micovic 2008], the significant reduction in these variables with OPCAB grafting translates into improved outcomes, possibly by reducing the intensity of the inflammatory response.

Other evidence suggests that although the EF improves over the long term after on-pump CABG, it is possible that the myocardial edema associated with ischemic cardiac arrest depresses the EF over the short term [Letsou 2011]. This depression is more pronounced with longer aortic cross-clamp times [Healey 2009] and is a possible reason why the patients who underwent CABG plus MVR required more inotropic support, a greater frequency of IAB*P* insertion, and longer times on a ventilator and in the ICU. Furthermore, substantial improvements in EF have been seen as early as 3 to 5 days after surgical revascularization with off-pump, compared with on-pump techniques [Letsou 2011], and could account for improved postoperative outcomes, particularly for the patients with IMR in this study who underwent OPCAB grafting.

We believe that another possible explanation for the improved outcomes in the group that underwent OPCAB plus MVR is that the patients had better myocardial protection, because all of the proximal anastomoses were made to the aorta before aortic cross-clamping. Therefore, better cardioplegia was delivered via the grafts, unlike in the group of patients who underwent CABG plus MVR.

One of the potential advantages of performing OPCAB grafting before performing a mitral valve intervention is that it aids in decision making regarding the mitral valve intervention, particularly in cases with moderate IMR. If the severity of MR improves (as assessed by intraoperative transesophageal echocardiography) under loading conditions after complete OPCAB revascularization, then mitral valve repair is not undertaken. On the other hand, persistence of the same degree of MR necessitates a mitral valve intervention.

One of the concerns regarding this strategy is that it may precipitate hemodynamic instability in patients with IMR and impairment in left ventricular function; however, only 1 patient in this study required conversion to CPB before completion of grafting. In this patient, obtuse marginal artery grafting was performed with an on-pump beating-heart strategy. We prophylactically insert an IAB*P* as an adjunct to safely perform OPCAB in cases deemed at high risk for hemodynamic instability. Our use of this practice is reflected in the results summarized in Table 1. An IAB*P* is a temporary device that has been well established for weaning patients from CPB and for postoperative low cardiac output syndrome. Because it has favorable hemodynamic effects on left ventricular performance and coronary arterial blood flow, preoperative IAB*P* support may have beneficial hemodynamic and anti-ischemic effects. There is evidence for beneficial use of a preoperative IAB*P* in CABG patients with a low EF undergoing nonelective operation, reoperation, and symptoms in New York Heart Association classes III and IV [Dietl 1996; Miceli 2009; Lavana 2010], and our results further validate the safety and efficacy of this approach in patients with IMR undergoing OPCAB grafting.

Similarly, concerns regarding incomplete revascularization with the OPCAB approach are not justified, because improvements in OPCAB technology in recent years have made grafting on inferior and lateral aspects feasible without significantly increasing risk and the chances of hemodynamic compromise. Furthermore, because CPB will be instituted in all cases of intervention on the mitral valve, the on-pump beating-heart approach can be adopted to ensure complete revascularization of the heart without the need for prolonged aortic cross-clamping, thus avoiding global myocardial ischemia and its untoward effects.

The main limitation of this study is the fact that it has emanated from a single institution and is a single surgeon's experience. Undoubtedly, any validation of the findings will require prospective multicenter studies. Another major criticism of the present study could be its much greater use of a preoperative IAB*P* in the OPCAB group, which potentially skews the data significantly in favor of OPCAB; however, use of an IAB*P* is a well-recognized strategy when undertaking high-risk OPCAB grafting and must be undertaken to ensure the safe conduct of surgery. Other limitations include its retrospective, observational nature and the small sample size.

Despite these limitations, our analysis shows that compared with the use of conventional CABG, the use of OPCAB grafting before repairing MR is associated with favorable in-hospital outcomes for patients undergoing surgery for IMR.

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