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Leveraging Innovation to Mitigate Risk During Heart Surgery

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Introduction

Innovation is not necessarily about the "next big thing" according to Mehta.[1] Instead, innovation can occur by combining existing technologies, developing small ideas that compound, or evolving to address problems that have arisen from previous innovations that yielded unpredictable consequences. Innovation in the field of cardiovascular surgery is no different. As the field becomes progressively less invasive through innovation, patients who require open cardiac surgery are increasingly complex and carry increased risk. Patients with ischemic cardiomyopathy at high risk for morbidity often require surgical revascularization and valve interventions; however, risk factors such as diminished ejection fraction, redo operation, and multiple comorbidities compound perioperative morbidity and operative mortality. This report will define high-risk cardiac surgery and discuss how surgeons can leverage innovation to mitigate risk.

Why Operate on High-Risk Patients?

The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1,212 patients with left ventricular ejection fraction (LVEF) of 35% or less and coronary artery disease suitable for surgical revascularization to coronary artery bypass grafting (CABG) or guideline-directed medical therapy (GDMT).[2] There was some crossover, but the initial analysis was done based on intention to treat. Among the 610 patients who were randomly assigned to the CABG group, 555 (91.0%) underwent CABG before completion of the trial. Among the 602 patients who were randomly assigned to the medical therapy group, 119 (19.8%) underwent CABG at any time before the completion of long-term follow-up. At median follow-up of 9.8 years, the CABG group had significantly lower risk of death from any cause with a hazard ratio (HR) of 0.84 (95% CI, 0.73-0.97, $P = .02$) as well as lower risk of death from cardiovascular cause ($P = .006$), hospitalization for heart failure ($P = .002$), nonfatal myocardial infarction (MI) ($P = .03$), or nonfatal stroke ($P = .03$) (Fig. 1).[2] The results remained consistent following analysis of crossovers. Of all patients who ultimately underwent CABG, 57% died during follow-up compared with 68% of those who underwent GDMT alone (HR, 0.75; 95% CI, 0.65-0.87; $P < .001$). The number needed to treat was 14 to save 1 life over 10 years with CABG.

Sun and coauthors[3] reviewed 12,113 patients with LVEF less than 35% and coronary disease appropriate for surgical revascularization who underwent percutaneous coronary intervention or CABG in Ontario, Canada. Propensity matching yielded 2,397 patients in each group. Patients who underwent percutaneous coronary intervention had significantly higher mortality rates (HR, 1.6; 95% CI, 1.3-1.7), cardiac morbidity (HR, 2.0; 95% CI, 1.9-2.2), repeat revascularization (HR, 3.7; 95% CI, 3.2-4.3), and hospitalization for MI (HR, 3.2; 95% CI, 2.6-3.8) or

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heart failure (HR, 1.5; 95% CI, 1.3-1.6) than did those who underwent CABG. These 2 studies support an aggressive surgical approach in patients with ischemic cardiomyopathy to improve long-term outcomes. Patients with ischemic cardiomyopathy live longer and have less cardiac morbidity with surgical revascularization. Stable patients with ischemic cardiomyopathy, however, have a higher 30-day mortality rate with CABG than with GDMT alone because of the acute surgical risk (4% vs 1% in STICH).[2] Thus, there is a need to explore options to decrease upfront morbidity and mortality in patients who require high-risk cardiac surgical intervention.

Abbreviations and Acronyms

CABG	coronary artery bypass grafting
CPB	cardiopulmonary bypass
GDMT	guideline-directed medical therapy
HR	hazard ratio
IABP	intra-aortic balloon pump
LCOS	low cardiac output syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
STICH	Surgical Treatment for Ischemic Heart Failure

What Defines High-Risk Patients?

Use of the Society for Thoracic Surgery risk calculator is often not accurate at the high end of risk for morbidity, especially in patients undergoing reoperative surgery.[4] Because of the magnitude of the data sets used to develop modern risk calculators, lesser common but very effective risk factors may be overshadowed by other more common risk factors and not reach statistical significance in multivariate analysis. For example, cirrhosis and liver failure have a profound effect on outcomes of any procedure, but neither is included in most cardiac surgery risk algorithms. In addition, frailty is a more recent addition to the preoperative evaluation of patients to determine fitness for transcatheter procedures; however, it does not affect risk prediction calculators for open procedures. High-risk cardiac surgery must be determined through assessment of a combination of objective and subjective criteria.

A survey of cardiac surgeons identified low LVEF as the most important risk factor, followed by elevated EuroSCORE, and redo surgery.[5] Elevated creatinine

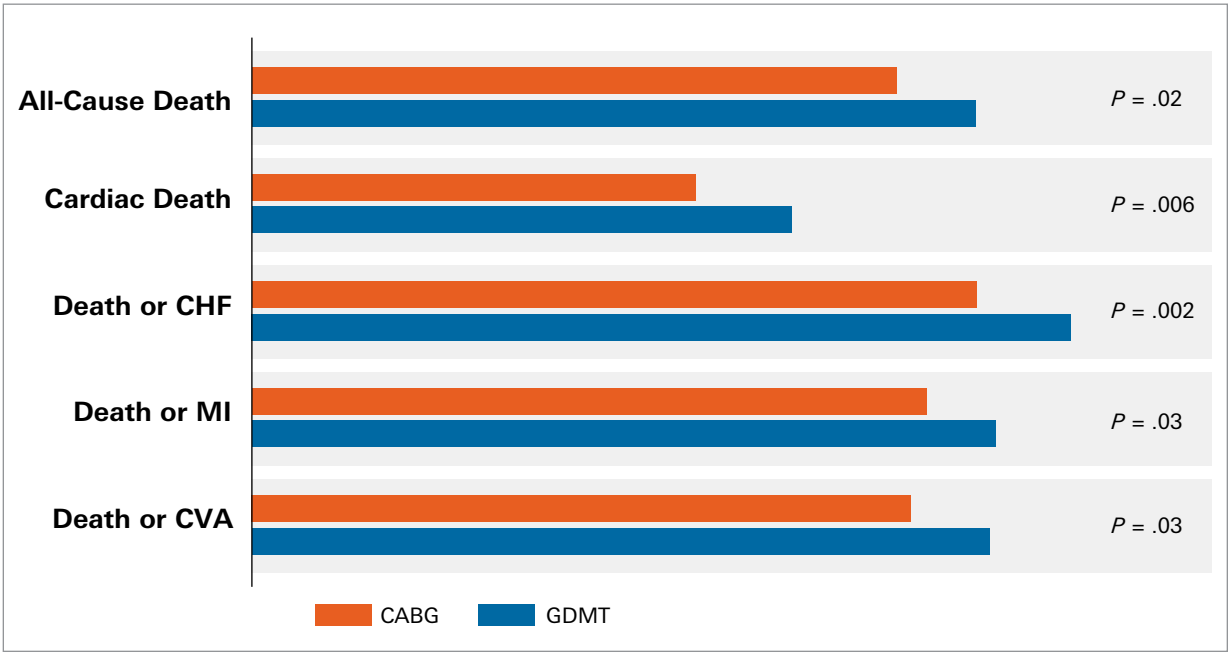

Fig. 1 Outcomes with CABG vs GDMT alone. Based on data from the STICH trial.[2] Adapted with permission from Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374(16):1511-1520. doi:10.1056/NEJMoa1602001

CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVA, cerebrovascular accident; GDMT, guideline-directed medical therapy; MI myocardial infarction; STICH, Surgical Treatment for Ischemic Heart Failure.

levels, tight left main stenosis with unstable angina, and elevated troponin and brain natriuretic peptide levels were also considered, but to a lesser degree. The Toronto General Hospital group reported a 9% incidence of low cardiac output syndrome (LCOS) among 4,558 patients undergoing CABG.[6] Low cardiac output syndrome was defined as the need for intra-aortic balloon pump (IABP) or inotropes for more than 30 minutes postoperatively to maintain a systolic blood pressure greater than 90 mm Hg and a cardiac index greater than 2.2 L/min/m^2. The mortality rate was much higher at 17% in those with LCOS than in patients with LCOS (17% vs 0.9%; $P < .001$). The most important risk factors for LCOS were: (1) LVEF less than 20% (27% incidence of LCOS in these patients; HR, 5.7), (2) reoperative surgery (25%; HR, 4.4), and (3) emergency operation (27%; HR, 3.7). Other significant factors included female sex (16%; HR, 2.5), diabetes (13%; HR, 1.6), age older than 70 years (13%; HR, 1.5), left main coronary artery disease (12%; HR, 1.4), recent MI (16%; HR, 1.4), and triple-vessel disease (10%; HR, 1.3). Strategies for optimization should focus on patients with poor left ventricular (LV) function and those undergoing reoperative surgery.

Strategies for Preoperative Optimization

Mitigation of Modifiable Comorbidities

Preoperative assessment of organ dysfunction should be performed. Correction of preoperative anemia may result in fewer blood transfusions during surgery. With moderate- to high-risk patients (EuroSCORE II >4), a hemoglobin level less than 11 g/dL is associated with a 3-fold increase in morbidity risk. Acute kidney injury may warrant a nephrology consult or further investigation of cardiorenal dysfunction. Assess for malnutrition with liver function tests and albumin or pre-albumin levels. It is important to assess if the patient is acutely decompensated from a cardiac perspective. Is there time for and benefit from outpatient GDMT? Is admission for preoperative right-sided pressure monitoring warranted? Consider preoperative inotropes and/or mechanical support.

Preoperative IABP

In patients with poor LV function, preoperative IABP can affect outcomes.[7-10] A 2011 meta-analysis evaluated preoperative IABP vs no IABP in 5 randomized, controlled trials that included patients with LVEF less than 30% to 40%, redo CABG, or unstable angina with tight left main stenosis.[7] They found a profound decrease in LCOS (HR, 0.14; 95% CI, 0.08-0.25; $P < .00001$) and mortality (HR, 0.18; 95% CI, 0.08-0.41; $P < .0001$) in patients with preoperative IABP. In one of these studies, Christenson et al[8] randomized patients to preoperative IABP vs no intervention and found that prophylactic IABP increased cardiac index from 1.52 L/min before IABP to 3.20 L/min on weaning from cardiopulmonary bypass (CPB). In the control group, cardiac index remained less than 2.0 L/min on weaning from CPB. The difference between the groups persisted up to 96 hours postoperatively, even following IABP removal, which generally occurred on postoperative day 1. There was no difference in the impact of prophylactic IABP whether it was placed intraoperatively before going on CPB or at 12 or 24 hours preoperatively; all were beneficial. Prophylactic IABP can also decrease the incidence of acute kidney injury by 46% and the need for kidney replacement therapy by 82%.[10] Prophylactic IABP is beneficial in high-risk cardiac patients by increasing myocardial perfusion during diastole; decreasing myocardial oxygen consumption, LV afterload, and LV wall tension; increasing cardiac output (generally by 0.5-1.5 L/min); and decreasing systemic vasoconstriction.

Preoperative Inotropic Support

Levosimendan is a calcium-sensitizer with inotropic and vasodilatory effects. Levin and colleagues[11] randomized 252 patients undergoing CABG with severely diminished LV function (LVEF less than 25% to 30%). Levosimendan or placebo was started 24 hours preoperatively. There was a 50% increase in cardiac index and 33% decrease in pulmonary artery pressures in the levosimendan group up to 48 hours postoperatively. Postoperative LCOS was more common in the control group (20.8% control vs 7.1% levosimendan; $P < .05$) as was mortality (12.8% vs 3.9%, respectively; $P < .05$). Fewer patients required additional inotropes (7.9% vs 58.4%; $P < .05$), vasopressors (14.2% vs 45.6%; $P < .05$), or an IABP (6.3% vs 30.4%; $P < .05$) in the levosimendan group than in the controls.

Mehta et al[12] performed a similar analysis, but with a higher LVEF cutoff of 35% or less. Compared with the study by Levin and colleagues[11] in patients with LVEF below 25%, they found no difference in the composite endpoint of death, kidney replacement therapy, perioperative MI, or use of a mechanical cardiac assist device between the levosimendan and control groups. Sub-

group analysis, however, demonstrated improved outcomes in patients undergoing isolated CABG compared with those undergoing isolated valve procedures or combined valve/CABG procedures.[13] In patients undergoing isolated CABG, the incidence of LCOS was lower with levosimendan (HR, 0.48; 95% CI, 0.30-0.76), and 90-day mortality improved (HR, 0.36; 95% CI, 0.11-0.64).

A study from John et al[14] found that both levosimendan and dobutamine improved cardiac index and ejection fraction and decreased serum creatinine in patients with acute decompensated heart failure. In addition, levosimendan reduced intensive care unit length of stay, whereas dobutamine reduced hospital length of stay. Guerrero-Orriach et al[15] similarly found that both levosimendan and dobutamine improved cardiac index and vascular tone in postoperative cardiac patients with LCOS, but levosimendan had a more beneficial effect on kidney function. Ventricular tachyarrhythmia has been the main adverse event with levosimendan. Greco et al16 performed a bayesian network meta-analysis of 46 trials that randomized 2,647 patients. They found that prophylactic levosimendan was associated with a decrease in mortality compared with placebo (HR, 0.48; 95% CI, 0.28-0.80), and the effect was greater than that with other inotropic agents. Dobutamine and milrinone were also effective, but to a lesser degree than levosimendan in their analysis.[16,17]

The Mount Sinai group in New York advocates preoperative hemodynamic optimization for high-risk patients undergoing mitral intervention.[18] Their practice is to admit high-risk patients for right-sided pressure monitoring, preoperative inotropic support, and diuresis. Milrinone is their current inotrope of choice. Optimization for 24 hours preoperatively decreased systolic pulmonary artery pressure by 33%, from 63 mm Hg to 39 mm Hg, with more effective diuresis. Patients lost an average of 3.7 kg preoperatively with short-term optimization.

Perioperative Mechanical Support

It is beyond the scope of this paper to describe in detail the differences between the varying forms of mechanical circulatory support; however, the TandemHeart (LivaNova) and Impella (Abiomed, Inc) systems are the 2 favored devices for temporary left-sided support when an IABP is contraindicated or would not provide enough support.[19,20] If right-sided heart failure is the main problem or adequate oxygenation cannot be achieved, full extracorporeal membrane oxygenation would be required. Left-sided support, however, is generally sufficient for prophylactic nonemergent surgical interventions. The TandemHeart is an extracorporeal centrifugal flow pump with its inflow cannula placed through the femoral vein and into the left atrium via a transseptal approach. The outflow cannula is inserted into the femoral artery, generally with a distal perfusion catheter to minimize ischemia to the leg. The TandemHeart improves hemodynamic and metabolic parameters over IABP in patients with intractable shock, although bleeding and limb ischemia are more prevalent with the TandemHeart than with the Impella device.

The Impella device is a nonpulsatile axial-flow pump that resides in the left ventricle and pumps blood from the ventricle into the aorta beyond the aortic valve. Although a low-flow percutaneous device (Impella CP) can be placed via the femoral artery (14F, flow of 2-3 L/min), only short-term (≤4 days) use is appropriate. The Impella 5.5 pump is the authors' preferred approach for prophylactic perioperative use. It is placed either preoperatively via a tunneled axillary chimney graft (surgically placed 10-mm Dacron conduit) or intraoperatively via a graft placed on the innominate artery. Two reports described satisfactory outcomes with the Impella 5.5 device for postcardiotomy syndrome[21,22]; however, the authors have started to place an Impella 5.5 device the day before high-risk CABG in patients with extreme lows of LVEF. Benke and associates[23] reported on 14 patients with mean ejection fraction of 21% undergoing cardiac surgery with a prophylactic high-flow Impella pump. Although they did not have a comparator group, they found prophylactic Impella pump use to be a safe approach with acceptable outcomes in these patients at high risk for morbidity.[23]

Key Considerations

High-risk surgical patients with multiple comorbidities and poor LV function present perioperative challenges beyond the requirements of a sound technical procedure. Preoperative optimization of modifiable risk factors is a key first step. Admission before surgery for right-sided pressure monitoring, initiation of inotropes, and diuresis is appropriate for patients who are acutely decompensated. Preoperative support with an IABP may be considered for patients with diminished LVEF, especially for patients undergoing CABG who will benefit from increased diastolic graft flow in addition to LV unloading and cardiac output support postoperatively.

Mechanical circulatory support with a temporary LV assist device is increasingly used and studied for prophylactic use in the extreme-risk patients. Prompt surgical intervention after correction of modifiable factors, coupled with surgical finesse and the use of appropriate innovative tools, will continue to advance the reach of cardiac surgery.

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