Editorial

Through the open door! Where has the ride taken us?

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There is no operation as complex, yet as fundamentally unchanged over time, as conventional coronary artery bypass grafting (CABG). This remarkable achievement is credited to the operation's adaptability to a wide variety of clinical settings; its reproducibility and durability while performed by a vast cadre of surgeons all across the world; and its proven track record for safety and effectiveness. A momentous effort, however, is evolving to redefine CABG. This paradigm shift has received a groundswell of support as advances in minimally invasive surgery in other areas, such as arthroscopy, laparoscopic cholecystectomy, and thoracoscopy, combined with an increasing focus on cost containment, have forever changed the milieu of the cardiac surgeon.

The clinical effectiveness of the left internal thoracic artery-to-left anterior descending coronary artery anastomosis combined with the considerable morbidity associated with conventional CABG provided the impetus for exploring alternative approaches to surgical revascularization. These approaches have all fallen under the general rubric of minimally invasive CABG. The clinical goals of minimally invasive CABG are interrelated and include (in order of importance): (1) achieving graft patency rates equal or superior to those of conventional CABG (avoid repeated revascularization); (2) decreasing incisional pain and discomfort (reduce invasiveness); (3) facilitating a more rapid return to normal activity levels (reduce invasiveness); (4) reducing the length of hospital stay (decrease complications); and (5) decreasing cost. Currently, the most widely practiced minimally invasive approach involves surgical revascularization on the beating heart through a median sternotomy incision, or off-pump coronary artery bypass grafting (OPCAB). Best industry estimates are that OPCAB, and other beating heart techniques, constituted approximately 24.7% of the 350,000 isolated CABG operations performed in 2001 (personal communication from Medtronic, Inc, Minneapolis, Minn, December 2001). Despite tremendous enthusiasm on the part of patients, industry, and the media, however, widespread adoption will not occur until OPCAB is validated through the explicit and conscientious assessment of current best evidence.

Accordingly, what is the current best evidence available relating to OPCAB? A logical and comprehensive approach to evaluating clinically relevant research incorporates many different types of evidence (including randomized clinical trials [RCTs], nonrandomized clinical trials [non-RCTs], and experimental data) and analyzes the information's content for consistency, coherence, and clarity. A useful metric for the assessment of clinical research is shown in Table 1.¹

In the hierarchy of clinical evidence, the RCT is generally considered the best approach to ascertain the value of a particular therapy. RCTs compare outcomes in a group of patients to which a test treatment (eg, OPCAB) has been applied with those observed in a comparable group of patients receiving a control treatment (eg, conventional CABG). Ideally, patients in the treatment and control arms are iden-

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TABLE 1. Grading of recommendations and levels of evidence*

First author	No. of patients	Angiograms	No. of grafts	Graft patency rate (%)	
Calafiore	122	67	54.9	185	98.5*
Mack	103	100	97	100	91.0*
Bull	40	NA		108	97.0†
Puskas	200	167	83.5	421	93.3*

TABLE 2. Angiographic graft patency rates after OPCAB

First author	No. of patients	Angiograms		No. of grafts	Graft patency rate (%)
		No.	%		
Calafiore	122	67	54.9	185	98.5*
Mack	103	100	97	100	91.0*
Bull	40	NA		108	97.0†
Puskas	200	167	83.5	421	93.3*

NA, Not available.

*FitzGibbon grade A (*J Am Coll Cardiol.* 1996;28:616-26).

†Definition of patency not given.

Table available in print only

*Adapted from Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. *Evidence Based Cardiology*. London: BMJ Books; 1998.

tical in every way such that any difference in outcomes between the two groups can be attributed exclusively to their respective treatments. Advantages of the RCT include adherence to the experimental method and the absence of selection bias. Disadvantages, however, include the considerable time, resources, and expense required to complete trials sufficiently large to demonstrate important differences in outcome, particularly when the observed incidence of differences in outcome is low (eg, operative mortality after surgical revascularization). Furthermore, the generalizability of the study's results beyond specific inclusion and exclusion criteria can be legitimately questioned. Therefore, much data regarding clinical outcomes is gained by observational studies including the propensity score computer-matched study by Sabik and associates² in this issue of the *Journal*.

In OPCAB, numerous studies have been conducted to address a variety of important clinical outcomes, including (1) early graft patency, (2) blood loss and blood transfusion requirements, (3) acute renal failure, (4) myocardial protection, (5) adverse neurologic events, (6) length of hospital stay, (7) morbidity, and (8) mortality.

Early Graft Patency

The major obstacle to achieving an effective coronary anastomosis in OPCAB is the translational motion of the beating heart. In OPCAB, translational motion is generally con-

strained by means of a mechanical stabilizer. Although adequate for immobilizing the left anterior descending coronary artery in most cases, the device's stabilizing efficiency is reduced in the lateral circumflex and inferior distributions and entails a significant learning curve. The few large studies of graft patency after beating heart CABG are mostly limited to the left internal thoracic artery-to-left anterior descending coronary artery anastomosis and provide only short-term follow-up (Table 2).³⁻⁶ Of 200 patients reported by Puskas and coworkers,⁵ 167 (83.5%) underwent a baseline angiographic evaluation before hospital discharge. Wide graft patency with unimpaired runoff (FitzGibbon grade A) to the target vessels was as follows: left anterior descending coronary artery, 145 of 160 (91%); obtuse marginal branch, 68 of 74 (92%); posterior descending artery, 65 of 68 (96%); and right coronary artery, 26 of 26 (100%).

Conclusion: In OPCAB, the left internal thoracic artery-to-left anterior descending coronary artery anastomosis can be accomplished with acceptable early graft patency in selected patients (grade B). Extrapolating this finding to anastomoses in the lateral and inferior distributions is premature at this time.

Blood Loss and Blood Transfusion Requirements

By exposing blood to the foreign materials present in the bypass circuit, cardiopulmonary bypass incites a systemic inflammatory response syndrome mediated by complement activation and cytokine release.⁷ This in turn promotes neutrophil activation, enhanced capillary permeability, interstitial edema, decreased systemic vascular resistance, and maldistribution of end-organ blood flow. This syndrome can manifest clinically as perioperative bleeding and acute renal failure. Three prospective RCTs have examined the issue of perioperative bleeding and the consequent transfusion requirement. Ascione and colleagues⁸ prospectively randomized 200 patients to OPCAB and conventional CABG. They observed that fewer OPCAB patients required blood transfusion (23% vs 52%, $P < .01$). van Dijk and associates⁹ prospectively randomized 281 patients and similarly reported fewer blood transfusions in the OPCAB group (3%

vs 13%, $P < .01$). Several non-RCTs have specifically addressed perioperative bleeding, and all have uniformly reported significantly less shed mediastinal blood loss after OPCAB: 148 ± 140 mL ($n = 60$) versus 386 ± 300 mL ($n = 55$), $P < .02^{10}$; 771 ± 66 mL ($n = 66$) versus 1084 ± 82 mL ($n = 60$), $P < .05^{11}$; 403 ± 407 mL ($n = 472$) versus 613 ± 453 mL ($n = 290$), $P < .001^{12}$; and 694 ± 692 mL ($n = 350$) versus 909 ± 617 mL ($n = 3171$), $P < .001^{13}$.

Conclusion: OPCAB favorably reduces blood transfusion requirements (grade A) and may reduce perioperative blood loss (grade B) compared with conventional CABG.

Acute Renal Failure

In a prospective study by Ascione and associates,¹⁴ 50 patients were randomized to OPCAB and conventional CABG. Renal glomerular filtration rate was measured by using creatinine clearance and computing the urinary microalbumin/creatinine ratio, and renal tubular function was assessed by measuring urinary *N*-acetyl glucosaminidase. Both laboratory determinants of renal function were favorably improved in the OPCAB group; however, the frequency of clinically important renal failure was not significantly different. Failure to detect a significant difference in this clinical end point can be attributed to its relatively small size, as well as the low observed incidence of acute renal failure in this population. In three non-RCTs, acute renal failure, defined as a greater than 50% increase in baseline creatinine or a need for dialysis, was significantly improved with OPCAB compared with conventional CABG: 3.85% ($n = 11,717$) versus 4.26% ($n = 106,423$), $P = .036^{15}$; 0.87% ($n = 346$) versus 2.75% ($n = 2,545$), $P = .036^{16}$; and 0% ($n = 406$) versus 1.5% ($n = 406$), $P = .030^{17}$.

Conclusion: OPCAB may favorably reduce the incidence of acute renal failure (grade B) after surgical revascularization compared with conventional CABG.

Myocardial Protection

Because it uses regional rather than global ischemia to provide a bloodless operative field, OPCAB has been postulated to cause less myocardial damage. Two prospective RCTs have demonstrated improved myocardial protection with OPCAB compared with conventional CABG based on lower peak creatine kinase MB fractions: $6.3 \mu\text{g/L}$ ($n = 11$) versus $15.1 \mu\text{g/L}$ ($n = 11$), $P = .008^{17}$ and $21 \pm 14 \mu\text{g/L}$ ($n = 25$) versus $30 \pm 6 \mu\text{g/L}$ ($n = 25$), $P = .04^{18}$; in a third RCT, improved myocardial protection was demonstrated by the creatine kinase MB fraction area-under-the-curve (164.0 vs 277.0 , $P < .01$).⁹

Conclusion: OPCAB may provide superior myocardial protection (grade A) and less myocardial necrosis compared with conventional CABG using cardioplegic arrest.

Adverse Neurologic Events

In a recent report by the Perioperative Ischemia Research Group, 2108 patients undergoing elective conventional CABG were prospectively evaluated for adverse neurologic events.¹⁹ Stroke was observed in 3.1% of patients and cognitive dysfunction or seizures were reported in 3.0%. Significantly, adverse neurologic events were associated with a 5- to 10-fold increase in mortality and doubling of the length of hospitalization. Also, between 30% and 47% of these patients were transferred to intermediate- or long-term care facilities compared with 8% of patients without adverse cerebral outcomes. The most powerful predictor of stroke was the presence of moderate or severe proximal aortic atherosclerosis detected by palpation. This finding provides compelling evidence that most postoperative strokes are related to cerebral microemboli arising from surgical manipulation of the ascending aorta; for example, during aortic cannulation and initiation of cardiopulmonary bypass, aortic crossclamping, and partial occlusion clamping. Thus, adverse neurologic events arising from the surgical manipulation of the aorta can significantly increase mortality, length of hospitalization, and cost of CABG.

In the only prospective RCT large enough ($n = 281$) to potentially detect a clinically important difference in postoperative stroke, van Dijk and colleagues⁹ did not detect a significant difference in the incidence of stroke after OPCAB compared with conventional CABG (0.7% vs 1.4%). Two large non-RCTs also failed to demonstrate significant improvement in stroke after OPCAB: 1.3% ($n = 1741$) versus 1.8% ($n = 6126$)²⁰ and 0.7% ($n = 406$) versus 1.2% ($n = 406$).² In contrast, two other large non-RCTs reported substantial improvement in stroke rates after OPCAB compared with conventional CABG: 0.8% ($n = 472$) versus 6.9% ($n = 290$), $P < .05^{12}$ and 1.25% ($n = 11,717$) versus 1.99% ($n = 106,423$), $P < .001^{15}$. Of importance, when attachment of saphenous vein grafts to the aorta was required, all of the referenced studies used partial aortic clamping to facilitate the proximal anastomosis. Hence, the benefit of completely avoiding aortic clamping by means of sutureless aorta-saphenous graft connectors remains speculative.²¹

Conclusion: On the basis of conflicting non-RCTs, the lack of concordant RCT data, and the failure to use newer technology that potentially can reduce cerebral microemboli, the benefit of OPCAB on adverse neurologic events remains uncertain.

Length of Hospital Stay and Overall Morbidity

The length of hospital stay after coronary artery bypass is a function of numerous factors relating to patient demographics (eg, age and sex); comorbid conditions (eg, diabetes and chronic obstructive pulmonary disease); severity of coronary heart disease (eg, New York Heart Association functional class, number of involved coronary arteries, and

TABLE 3. Comparison of observed and expected overall morbidity

First author	OPCAB		CABG		<i>P</i> value*
	Observed (%)	Expected (%)	Observed (%)	Expected (%)	
Plomondon	8.80	13.20	14.00	11.90	<.05
Cleveland	9.24	11.66	12.15	11.88	<.0001

OPCAB, Off-pump coronary artery bypass; CABG, coronary artery bypass grafting.

*Compares risk-adjusted overall morbidity.

degree and location of arterial stenoses); and postoperative morbidity (eg, atrial arrhythmia, prolonged inotropic support, prolonged mechanical ventilatory support, and bleeding).⁵ In the prospective study by van Dijk and colleagues,⁹ 281 patients were randomized to OPCAB or conventional CABG. OPCAB was associated with a significantly reduced length of hospital stay (6 days vs 7 days, $P < .01$). Several non-RCTs using contemporaneous control groups have also demonstrated a substantial decrease in hospital stay between OPCAB and conventional CABG: 3.9 ± 2.6 days ($n = 200$) versus 5.7 ± 5.3 days ($n = 1000$), $P < .001^5$; 4.0 ± 1.8 ($n = 472$) versus 4.7 ± 1.8 ($n = 290$), $P < .001^{13}$; 4.1 ± 1.6 ($n = 185$) versus 5.4 ± 2.4 ($n = 67$), $P < .001^3$; and 6.1 ± 3.6 ($n = 350$) versus 7.1 ± 6.4 ($n = 3171$), $P < .001^{13}$.

Two large non-RCTs examined the overall morbidity after OPCAB compared with conventional CABG.^{15,22} Both studies demonstrated clear superiority of OPCAB in reducing overall risk-adjusted morbidity (Table 3).

Conclusion: OPCAB is associated with shortened length of hospital stay (grade A) and may favorably reduce overall morbidity (grade B) compared with conventional CABG.

Mortality

Similar to postoperative morbidity, mortality after coronary bypass grafting is dependent on numerous factors, including patient demographics, comorbid conditions, coronary heart disease severity, and postoperative morbidity. Moreover, a few studies have implicated the use of cardiopulmonary bypass with hospital mortality.^{5,23} In the prospective RCT by van Dijk and coworkers,⁹ the 30-day mortality between OPCAB and conventional CABG arms was not significantly different: 0% ($n = 142$) versus 0% ($n = 139$). Among several large non-RCTs of primary coronary artery bypass, hospital mortality was improved with OPCAB in two studies: 1.4% ($n = 919$) versus 3.0% ($n = 924$), $P = .016$,²⁴ and 2.6% ($n = 472$) versus 8.7% ($n = 290$), $P < .001$.¹² However, mortality was not significantly improved in two others.^{2,13} Risk-adjusted mortality was examined in four large non-RCTs.^{15,20,22,25} Three studies suggested that OP-

TABLE 4. Comparison of observed and expected mortality

First author	OPCAB		CABG		<i>P</i> value*
	Observed (%)	Expected (%)	Observed (%)	Expected (%)	
Hernandez	2.54	2.67	2.57	2.67	.567
Plomondon	2.70	4.40	4.00	3.90	.101
Kshetry	0.74	2.70	2.13	2.30	.484
Cleveland	2.32	2.88	2.94	2.87	.001

NS, Not significant.

*Compares risk-adjusted overall morbidity.

CAB was safe and not associated with increased mortality, whereas one study demonstrated significant improvement in risk-adjusted mortality (Table 4).

Of note, two small non-RCTs focused primarily on the differences in operative mortality among high-risk subgroups of patients—reoperations²⁶ and predicted operative mortality greater than 5%.¹³ In both studies, OPCAB was associated with significantly improved observed mortality compared with conventional CABG: 1.0% ($n = 41$) versus 10.0% ($n = 91$), $P = .03$, and 7.7% ($n = 39$) versus 28.5% ($n = 123$), $P = .008$.

Conclusion: The operative mortality associated with OPCAB is no worse and may be significantly better than that accompanying conventional CABG, particularly in certain high-risk subsets (grade B).

Six years ago, Lytle²⁷ surveyed the “state of the science” of minimally invasive cardiac surgery. He correctly forecast that “the concepts of less invasive surgery will strongly influence adult cardiac surgery over the next decade” and warned about safety and the extent of compromise in the operative result that is acceptable with the following caution:

The door’s open but the ride it ain’t free.

—B. Springsteen

We are now 6 years down this road and indeed the practice adult cardiac surgery has significantly changed. As one views success of catheter-based revascularization and the advent of drug-eluting stents promising to diminish restenosis on the horizon, one must constantly re-evaluate the role surgical revascularization will play (now less than 30% of all coronary revascularizations). However, the continued success of coronary artery bypass surgery is maintained by minimizing procedural trauma without compromising long-term outcomes in a user-friendly manner that is widely applicable and teachable.

To further quote Lytle’s bard from *Thunder Road*:

We have one last chance to make it real.

—B. Springsteen

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