

Simultaneous hybrid coronary revascularization reduces postoperative morbidity compared with conventional off-pump coronary artery bypass

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The treatment of multivessel coronary artery disease with the simultaneous hybrid procedure, a minimally invasive technique for revascularization, provides for clinical outcomes and patient satisfaction that are very competitive with those of traditional off-pump coronary artery bypass. In addition, local activation of inflammation and coagulation is minimized, perhaps because of less myocardial manipulation and regional bouts of warm ischemia.

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Objectives: Less-invasive options are available for surgical treatment of multivessel coronary artery disease. We hypothesized that stenting combined with grafting of the left anterior descending artery with the left internal thoracic artery through a mini-thoracotomy (hybrid procedure) would provide the best outcome.

Methods: Patients with equivalent numbers of coronary lesions (2.8 ± 0.4) underwent either hybrid ($n = 15$) or off-pump coronary artery bypass through a sternotomy ($n = 30$). Early and 1-year outcomes were compared. Blood drawn from the aorta and coronary sinus immediately postoperatively was analyzed for activation of coagulation (prothrombin fragment 1.2 and activated Factor XII), myocardial injury (myoglobin), and inflammation (interleukin 8) by using an enzyme-linked immunosorbent assay. Target-vessel patency was determined by means of computed tomographic angiographic analysis.

Results: The hybrid procedure was associated with significantly shorter lengths of intubation and stays in the intensive care unit and hospital and perioperative morbidity ($P < .05$). Intraoperative costs were increased but postoperative costs were reduced for the hybrid procedure compared with off-pump coronary artery bypass through a sternotomy. As a result, overall total costs were not significantly different between the groups. After adjusting for potential confounders, assignment to the hybrid group was an independent predictor of shortened time to return to work ($t = -2.12$, $P = .04$). Patient satisfaction after the hybrid procedure, as judged on a 6-point scale, was greater versus that after off-pump coronary artery bypass through a sternotomy. Finally, the hybrid procedure showed significantly reduced transcardiac gradients of markers of coagulation, myocardial injury, and inflammation and a trend toward significant improvement in target-vessel patency.

Conclusions: Perhaps because of reduced myocardial injury, inflammation, and activation of coagulation, patients undergoing the hybrid procedure had better perioperative outcomes and satisfaction, with excellent patency at 1 year's follow-up. These promising preliminary findings warrant further investigation of this procedure.

Despite major improvements in stent technology, the left internal thoracic artery (LITA) bypass graft remains the superior long-term option for treating a stenosis of the left anterior descending coronary artery (LAD).^{1,2} Compared with a stent, the LITA graft is resistant to thrombosis and atherosclerosis and provides protection from progression of proximal coronary artery disease (CAD). A growing list of less-invasive options has become available that exploit the benefit of the LITA, including off-pump coronary artery bypass grafting (CABG) through a sternotomy (OPCAB) or multivessel revascularization through a small thoracotomy.³

A third alternative, percutaneous coronary intervention (PCI)/stenting combined with surgical LITA to LAD grafting through a minithoracotomy (the hybrid procedure), has

Abbreviations and Acronyms

| | |
|-------|---|
| ACT | = activated clotting time |
| CABG | = coronary artery bypass grafting |
| CAD | = coronary artery disease |
| CS | = coronary sinus |
| CT | = computed tomography |
| ELISA | = enzyme-linked immunosorbent assay |
| F1.2 | = prothrombin fragment 1.2 |
| ICU | = intensive care unit |
| LAD | = left anterior descending coronary artery |
| LITA | = left internal thoracic artery |
| MACE | = major adverse cardiac event |
| NYHA | = New York Heart Association |
| OPCAB | = off-pump coronary artery bypass grafting through a sternotomy |
| PCI | = percutaneous coronary intervention |
| SVG | = saphenous vein graft |

theoretic advantages. Stents substitute for the saphenous vein graft (SVG) as a bypass conduit, and LITA grafting through a minimally invasive approach minimizes surgical morbidity. This hybrid approach has not been widely adopted because of a number of practical concerns: the need for close cooperation of surgical and interventional groups, the logistic concerns of timing and sequencing of the procedures, and the use of aggressive anticoagulation in the surgical patient.

As a result of these challenges, the status quo for the surgical treatment of multivessel CAD is to perform a sternotomy for bypass grafting of a single LITA and multiple SVGs. At our institution, the surgical and interventional portions of the hybrid procedure have been completed simultaneously in a single operative suite. The purpose of this study was to compare the perioperative and 1-year outcomes of this state-of-the-art approach to the hybrid procedure compared with those of standard OPCAB.

Materials and Methods**Patient Selection and Enrollment**

Fifteen consecutive patients underwent the simultaneous hybrid procedure at our institution from January 2005 through December 2006. Using a prospective case-controlled study design, we matched a parallel control group of 30 patients who underwent OPCAB according to demographics, risk factors, comorbidities, coronary anatomy, medical therapy, and operative surgeon (RP). These matching criteria included known risk markers for outcomes with surgical revascularization (Table 1). Inclusion criteria for the hybrid procedure were the presence of multivessel CAD that involved greater than 70% LAD obstruction judged a suitable surgical target and the presence of a non-LAD coronary lesion (or lesions) suitable for PCI, as adjudicated by 2 interventionalists (BR and DZ) and 1 surgeon (RP). Hemodynamic instability, acute coronary syndromes, or situations in which complete revascularization was not possible served as exclusion criteria for the hybrid procedure. Patients with chronic renal insufficiency (creatinine value, >2.0 mg/dL) and allergy to radiographic contrast were also excluded from enrollment.

TABLE 1. Patient characteristics

| | Hybrid procedure (n = 15) | OPCAB (n = 30) | P Value |
|---|------------------------------|-------------------|---------|
| Age (y) | 61 ± 10 | 65 ± 10 | NS |
| BMI | 29 ± 13 | 27 ± 5 | NS |
| COPD | 13% | 10% | NS |
| Current smoker | 27% | 33% | NS |
| Diabetes | 27% | 40% | NS |
| Ejection fraction | 47 ± 14 | 45 ± 14 | NS |
| Male sex | 73% | 63% | NS |
| History of familial coronary artery disease | 33% | 40% | NS |
| Hypercholesterolemia | 73% | 87% | NS |
| Hypertension (>90 and/or >140 mm Hg) | 87% | 80% | NS |
| No. of diseased vessels | 2.7 ± 0.5 | 2.8 ± 0.4 | NS |
| NYHA class | 2.7 ± 1 | 3.1 ± 0.9 | NS |
| Peripheral vascular disease | 33% | 27% | NS |
| Previous heart surgery | 7% | 7% | NS |
| Previous myocardial infarction | 67% | 57% | NS |
| Previous stroke | 7% | 0% | NS |
| Ratio of revascularized/ diseased vessels | 0.93 ± 0.14 | 0.97 ± 0.1 | NS |
| Baseline medications | | | |
| ACE inhibitor | 33% | 47% | NS |
| Aspirin | 93% | 87% | NS |
| β-Blocker | 100% | 80% | NS |
| Intravenous heparin | 40% | 60% | NS |
| Intravenous nitrates | 0% | 7% | NS |

OPCAB, Off-pump coronary artery bypass grafting through a sternotomy; NS, not significant; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

Patients were followed up daily during hospitalization and then at 1 year as an outpatient to assess mortality, target-vessel patency, and other outcomes. Demographics, preoperative risk factors and medications, and intraoperative and postoperative data were prospectively recorded into a relational database. All patients provided informed consent to be enrolled in the study (UMB IRB no. 25350).

Surgical Procedure

OPCAB. After median sternotomy, the LITA was procured and the saphenous vein was harvested by using an endoscopic approach (VasoView6; Guidant Systems, Inc, Minneapolis, Minn). Proximal anastomoses were performed with a partial occluding aortic clamp. All distal anastomoses were performed on the beating heart facilitated by suction-based exposure and stabilizing devices (Octopus 4.3; Medtronic, Inc, Minneapolis, Minn).

Hybrid procedure. Patients were placed in a supine position with the left chest slightly elevated and intubated with a double-lumen endotracheal tube to allow for collapse of the left lung. An 8- to 10-cm anterior lateral thoracotomy in the fourth intercostal

space was created to expose the in situ LITA with the assistance of the LITA lift retractor (Genzyme Cardiovascular, Cambridge, Mass). The conduit was then harvested as a pedicle. LITA-to-LAD CABG was performed through a small thoracotomy without the use of cardiopulmonary bypass. Selective use of an intracoronary shunt was used based on changes, which were suggestive of anterior myocardial ischemia. A stabilizer (Octopus 4.3; Medtronic, Inc) was then secured over the LAD, and the anastomosis was performed on the beating heart. Additional targets were revascularized by using PCI performed immediately after completion of LITA grafting in a specially designed operating suite outfitted with fluoroscopic equipment. In most cases the thorax was closed before PCI. However, for those patients with higher levels of bleeding, the thorax was left open until the completion of PCI to allow a second evaluation of hemostasis. Access was achieved through the femoral artery by using 6F guiding catheters. Guidewire and stent selection, along with predilation and postdilation, were left to the discretion of the operator. Drug-eluting stents were implanted in all patients. Both the Cypher Sirolimus-eluting stent (Cordis Corp, Miami Lakes, Fla) and the Taxus Paclitaxel-eluting stent (Boston Scientific, Inc, Natick, Mass) were used.

In both groups unfractionated heparin was administered intraoperatively to obtain a kaolin-based activated clotting time (ACT) of greater than 300 seconds and a heparin level of greater than 2 IU/mL, according to the heparin-protamine titration assay (HMS Heparin Assay Cartridges; Medtronic, Inc). Also, aspirin (325 mg by mouth daily) was given to both groups preoperatively and within 6 hours postoperatively. Heparin was reversed with half the recommended dose of protamine for OPCAB. For patients undergoing the hybrid procedure, heparin was not reversed, and a loading dose of 300 mg of clopidogrel was administered through a nasogastric tube on arrival to the intensive care unit (ICU), followed by 75 mg daily thereafter. GPIIb/IIIa antagonists were not used.

Clinical Outcomes and Total Cost Assessment

During hospitalization, major adverse cardiac events (MACEs) were monitored by determining mortality, perioperative myocardial infarction on the basis of new Q-waves or troponin I levels of greater than 5 times normal values, clinically evident stroke, or the need for coronary artery reintervention. Intraoperative blood loss was quantified by using a Cell Saver device. Chart review was conducted to assess intraoperative packed red blood cell transfusions, intraoperative cardiac index and central venous pressure, postoperative length of intubation, daily serum creatinine level, length of ICU and hospital stay, and peak pain score (scale, 0–10).

At 1 year after the operation, patients were interviewed, and their medical records were reviewed to determine the following outcomes: (1) mortality, (2) MACEs at 1 year, (3) New York Heart Association (NYHA) angina classification, (4) duration of pain from surgical incision persisting after the operation, (5) length of time to return to work or normal activities, and (6) overall satisfaction with the procedure based semiquantitatively on a score of 1 to 6, with 1 being dissatisfied and 6 being completely satisfied. Total costs were obtained for each group by using the hospital's database.

Regional Hypercoagulability, Myocardial Ischemia, and Inflammation

Differences in regional hypercoagulability, ischemia, and inflammation were measured by collecting arterial ("aortic") and coronary

sinus (CS) blood samples 30 minutes after heparin reversal into tubes containing 3.2% citrate. CS blood was obtained through a heparin-bonded catheter (Cook, Inc) placed into the CS through transjugular access for patients undergoing the hybrid procedure or by means of direct external puncture of the CS with an 18-gauge butterfly needle for patients undergoing OPCAB. Platelet-poor plasma was obtained by means of rapid centrifugation (2000g) and stored at -80°C . Thrombin formation was assayed on the basis of the level of prothrombin fragment 1.2 (F1.2) by means of enzyme-linked immunosorbent assay (ELISA; Dade Behring, Marburg, Germany), and the activity of the contact activation pathway was evaluated by assaying activated Factor XII (American Diagnostica, Inc, Stamford, Conn). Cardiac myoglobin and interleukin 8 releases were determined by comparing aortic versus CS levels in the blood samples by means of ELISA (Life Diagnostics, Inc, West Chester, Pa, and Bender MedSystems, Vienna, Austria, respectively). Comparison of these markers in the CS ($F1.2_{CS}$) to a simultaneously obtained aortic ($F1.2_{Ao}$) sample allowed for calculation of the percentage of transcardiac change, as follows: $(F1.2_{CS} - F1.2_{Ao}) / F1.2_{Ao} \times 100$. Additionally, systemic blood samples were obtained on postoperative day 1 to assess troponin I levels by means of ELISA (Life Diagnostics, Inc).

Target-vessel Patency

In addition, target-vessel patency was assessed by using 16-channel CTA (420-ms rotation with 100–150 mL of contrast agent administered intravenously at 5 mL/s and retrospective electrocardiographic gating; Philips MX8000, Cleveland, Ohio) at both 5 days (postoperative) and 1 year (follow-up) after the operation. Patency at both time points was defined as any flow through the entire graft or stent, regardless of the presence of stenosis. The graft was classified as nonpatent if a stump was seen or if there was no contrast in an area known by operative report to contain a graft, as previously described.⁴ The diagnosis of stent thrombosis was based on screening computed tomographic (CT) angiographic analysis, clinical signs/symptoms of ischemia confirmed as a result of stent closure by means of conventional angiographic analysis, or both.

Statistical Methods

The primary end point of this trial was a comparison of postoperative morbidity between the 2 groups. We performed univariate analysis to compare potential confounders of the relationship between group assignment and time to return to work/normal activities using the Student *t* test and the Fisher exact test for continuous and dichotomous variables, respectively. Variables with a *P* value of less than .1 between groups were included in a stepwise logistic regression model, with the dependent variable being categorical (time to return to work of >1 or <1 month) and independent variables that were both continuous (age, body mass index, and preoperative creatinine value) and categorical (NYHA classification, diabetes, and number of diseased vessels). Statistical analyses were performed by a biostatistician (AJ).

Results

Baseline patient characteristics were similar between the 2 groups in all assessed preoperative and intraoperative variables (Table 1). All patients received a LITA graft, and additional targets were addressed per group assignment. The

hybrid group received 22 stents (11 Sirolimus-eluting stents and 11 Taxus Paclitaxel-eluting stents), and the OPCAB group received 40 SVGs, 6 right internal thoracic artery grafts, and 6 radial artery grafts. At 1 year, 80% of patients in each group successfully completed the follow-up, and 100% returned to assess target-vessel patency.

Early Clinical Outcomes and Hospitalization Costs

There were no mortalities and no readmissions during the postoperative period in either group. Postoperative MACEs developed in no patients in the hybrid group and in 7 patients in the OPCAB group because of 6 myocardial infarctions and 1 stroke (0% vs 23%, $P = .05$). Compared with the OPCAB group, patients in the hybrid group maintained better intraoperative cardiac indices (35% vs 23% decrease from baseline, $P = .08$) and less of an increase in central venous pressure (50% vs 17% increase from baseline, $P = .01$). Patients in the hybrid group also required less red blood cell transfusions (0.2 ± 0.4 vs 1.4 ± 1.4 U, $P \leq .0001$), shorter intubation times (1.3 ± 3.4 vs 20.6 ± 25.7 hours, $P \leq .001$), and shorter lengths of stay in the ICU (0.98 ± 0.42 vs 2.42 ± 1.57 days, $P \leq .0001$) and hospital (3.7 ± 1.4 vs 6.4 ± 2.2 days, $P \leq .0001$). Postoperative renal insufficiency, defined as an increase of serum creatinine values more than 25% above baseline values, was noted in 3 (10%) patients after OPCAB but was not seen after the hybrid procedure.

These differences resulted in a significant reduction in costs for the patients undergoing the hybrid procedure in the postoperative period. In contrast, OPCAB showed a significant reduction in intraoperative costs, largely because of shorter operative times and the use of autologous grafts rather than stents ($\$9819 \pm \2229 vs $\$14,691 \pm \2967 , OPCAB vs hybrid procedure; $P < .001$). As a result of this difference in intraoperative versus postoperative costs, there was no significant difference in the overall hospital costs between the groups (Figure 1). Maximum pain scores, ranging from none (0) to the most severe ever experienced (10), were higher after minithoracotomy (hybrid procedure) than sternotomy (OPCAB; 8.6 ± 1.8 vs 6.8 ± 2.7 , $P = .01$).

As the result of different protocols for heparin reversal, there was a significant difference in the ACT measured immediately at the completion of the case for patients in the hybrid group compared with those in the OPCAB group (235 ± 56 vs 132 ± 23 seconds, $P < .001$).

One-year Outcomes

At 1 year's follow-up, there was no mortality in either group. MACEs were noted in 1 (7%) of the patients in the hybrid group and in 7 (23%) of the patients in the OPCAB group as a result of 1 reintervention required for a patient in the hybrid group for stent thrombosis. This patient was also the only patient in either group with angina at 1 year (mean NYHA angina classification: 0.2 vs 0, hybrid procedure vs OPCAB). The duration of the time that it took for pain to completely

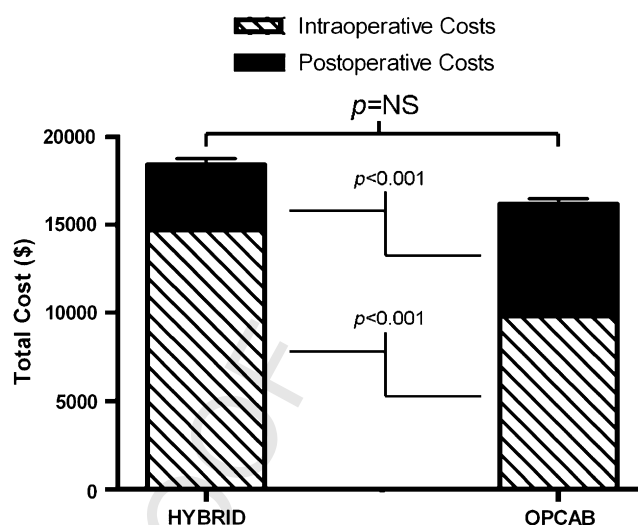


Figure 1. Although a significant increase in operative costs was noted in the hybrid group ($P < .001$), total average costs were not significantly different between the groups. This was the result of significantly lower postoperative costs ($P < .001$) in the hybrid group, with its reduction in transfusions and lengths of intensive care unit and hospital stay versus the off-pump coronary artery bypass grafting through a sternotomy (OPCAB) group. NS, Not significant.

resolve was shorter for the hybrid procedure versus OPCAB (10.3 ± 10.9 vs 45.5 ± 33.6 days, $P = .004$). Overall satisfaction scores were also higher after the hybrid procedure (Figure 2), with significantly more patients reporting that they were completely satisfied (83% vs 42%, hybrid procedure vs OPCAB; $P < .001$).

Patients returned to work or normal activities quicker after the hybrid procedure versus OPCAB (Figure 3). The average time to return to work in patients with a sternotomy was 4.4 ± 3.1 months, which is significantly greater than the 1.75 ± 1.0 months for patients with a minithoracotomy ($t = 3.68$, $P = .0008$). There was a significant relationship between group assignment (ie, hybrid vs OPCAB) and returning to work before 1 month (χ^2 statistic = 7.08, $P = .008$). The odds of returning to work at less than 1 month were significantly better for the hybrid procedure versus OPCAB after adjusting for potential confounders (odds ratio, 7.60; 95% confidence interval, 1.61–35.91; $P = .01$). On multivariate regression analysis, the choice of procedure was a significant predictor of the time to return to work ($t = -2.12$; standard error = 0.96; $P = .04$; 95% confidence interval, -4.04 to -0.11). None of the other variables analyzed were significant predictors.

Regional Hypercoagulability, Myocardial Ischemia and Inflammation

There was significantly less intraoperative blood loss during the hybrid procedure versus OPCAB (579 ± 406 vs $1091 \pm$

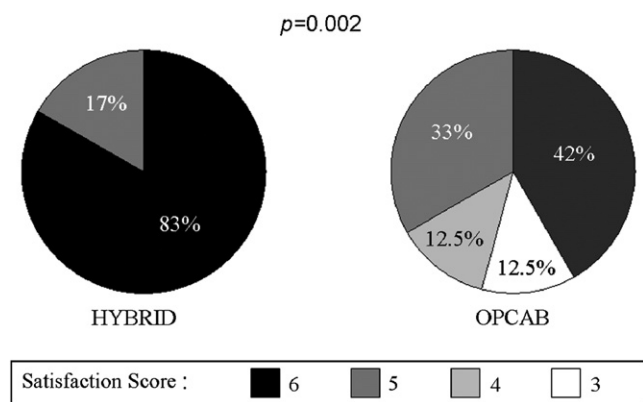


Figure 2. At 1 year, patients reported their overall satisfaction with the procedure on a 1- to 6-point scale, ranging from dissatisfied to completely satisfied. The hybrid group reported a significantly higher mean level of satisfaction compared with the off-pump coronary artery bypass grafting through a sternotomy (OPCAB) group, with 83% of patients in the hybrid group versus 42% of patients in the OPCAB group completely satisfied ($P \leq .001$, Fisher exact test).

601 mL, $P = .004$). Despite better hemostasis, the transcardiac gradients of markers of thrombosis (F1.2 and activated Factor XII), ischemia (myoglobin), and inflammation (interleukin 8) were all significantly reduced after the hybrid procedure versus OPCAB (Figure 4). Troponin I levels on day 1 were significantly less in patients undergoing the hybrid pro-

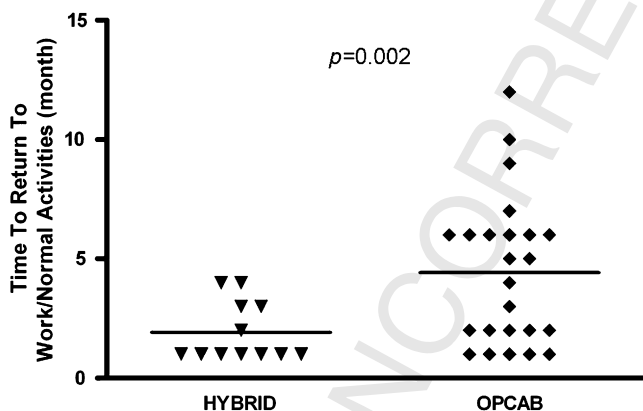


Figure 3. The time for each patient to return to work (or normal activity for those who do not work) was monitored in each patient group. The period required for patients in the hybrid group was significantly shorter compared with that of the off-pump coronary artery bypass grafting through a sternotomy (OPCAB) group. After adjusting for potential confounders with a multivariate analysis, assignment to the hybrid group was found to be an independent predictor of a shorter length of time to return to work/normal activities ($t = -2.5$, $P = .02$).

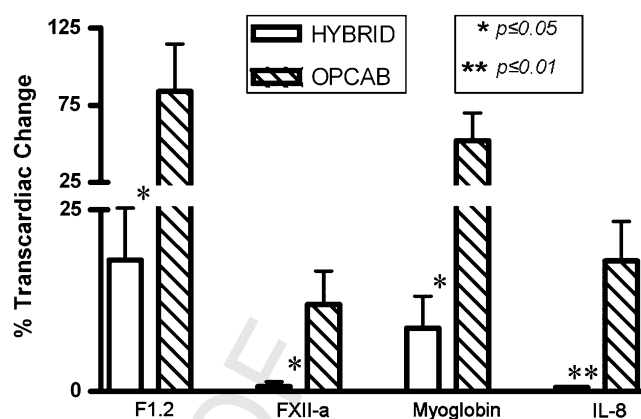


Figure 4. Myocardial ischemia, inflammation, and activation of coagulation were analyzed within the heart after hybrid versus off-pump coronary artery bypass grafting through a sternotomy (OPCAB) procedures by obtaining aortic and coronary sinus blood samples 30 minutes after case completion. The transcardiac gradients of serum levels of markers of thrombin formation (prothrombin fragment 1.2 [F1.2]), activation of the intrinsic coagulation cascade (activated Factor XII [FXII-a]), ischemia (myoglobin), and inflammation (interleukin 8 [IL-8]) were all significantly reduced after the hybrid procedure versus OPCAB.

cedure versus those undergoing OPCAB (1.4 ± 0.7 vs 2.8 ± 2.6 ng/mL, $P < .03$).

CT Angiographic Follow-up

Conventional angiography performed during each case intraoperatively and CT angiography performed before hospital discharge confirmed target-vessel patency for all patients in the hybrid group. PredischARGE CT angiographic results obtained in the OPCAB group documented patency in 77 (94%) of 82 grafts, with early failure noted in 1 right internal thoracic artery graft, 1 radial artery graft, and 3 SVGs. At 1 year, a single stent failed in the hybrid group versus 7 additional SVG failures in the OPCAB group (97% vs 85% overall patency, Figure 5).

Discussion

OPCAB was initially touted as a less-invasive alternative to the traditional on-pump technique, yet direct comparisons of outcomes between these methods have been surprisingly similar. The hybrid procedure has been established in prior reports as a viable alternative to open-sternum CABG for selected patients with multivessel disease.⁵⁻⁷ We performed stenting and bypass simultaneously using a specially outfitted hybrid operating suite at our center. A variety of better outcomes were noted in patients treated with this state-of-the-art approach compared with OPCAB, including reduced lengths of intubation and ICU stay, less transfusions, quicker resolution of pain, earlier return to work/normal activities,

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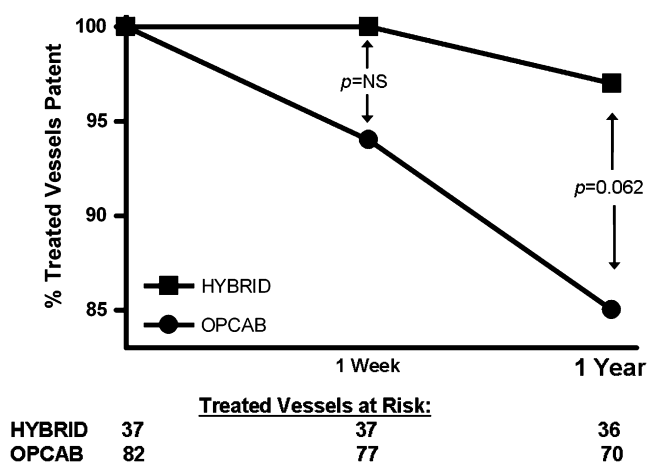


Figure 5. An analysis of early graft and stent patency was obtained by using multichannel computed tomographic angiography before discharge and again at 1 year. This analysis showed a trend toward better midterm target-vessel patency for the hybrid group. Both groups received 100% follow-up at both time points. **OPCAB, Off-pump coronary artery bypass grafting through a sternotomy; NS, not significant.**

and greater overall satisfaction with the surgical experience. Although target-vessel patency at 1 year's follow-up was excellent in both groups, cardiac release of hypercoagulability markers was reduced after the hybrid procedure, suggesting a decreased risk for coronary thrombotic events in these patients. Our experience suggests that an encouraging array of advantages might follow the adoption of a less-traumatic technique, such as the hybrid procedure, that have not yet materialized by merely avoiding cardiopulmonary bypass.

Finding reduced postoperative costs for our hybrid group was notable given that OPCAB represents the best available evidence-based approach for cost savings.^{8,9} It is possible that enthusiasm for the hybrid procedure biased the management of variables that are often based on subjective judgments and also are important drivers of hospital costs, such as time for extubation, length of stay, and red blood cell transfusion. We believe the risk of this type of bias was minimized by the fact that our study was performed in the context of decreasing reimbursements for CABG, which creates a strong incentive to limit costs regardless of the approach. The differences in postoperative costs were offset by higher intraoperative costs for the hybrid procedure because of longer operative times and the costs of coated stents. Further reductions in operative times because of the learning curve of minimally invasive surgery and the recent transition to less-costly bare-metal stents to avoid delayed thrombosis might help improve total costs in our ongoing analysis.

Despite higher pain scores after minithoracotomy versus sternotomy, the odds of patients in the hybrid group returning to work within the first month were 7-fold better than in the

OPCAB group, even after adjusting for potential confounders. Multivariate techniques cannot adjust for all the factors that influence a subjective end point such as the appropriate time to return to work. Although not detected in interviews, patients, their providers, or both could have had the preconceived notion that the hybrid procedure is more likely than OPCAB to allow a quicker return to normalcy. However, early return to work was the stated goal of a vast majority of the patients in this cohort. Recovery time defined in this broader context provides an important benchmark for programmatic success from the standpoint of the patient and helps to justify the use of a strategy that is not the standard of care for triple-vessel CAD.

More rapid recovery for the hybrid cohort suggests that factors other than pain play a role in their quicker recovery. Less blood transfusions and reduced systemic inflammation have been linked to improved postoperative morbidity in a number of studies comparing minimally invasive and conventional surgery and likely play a role in outcomes after the hybrid procedure. In addition, the degree of cardiac manipulation varies between the hybrid procedure, where the heart is left in its native position, versus OPCAB, which frequently requires the heart to be rotated into positions that compromise hemodynamics, as noted in our patients. In addition, coronary occlusion for the hybrid procedure is limited to that required for placement of a single LAD graft and less than 20-second intervals for stenting. OPCAB requires 8- to 12-minute periods of coronary occlusion during each of 3 to 4 distal anastomoses (total ischemic time, 25–40 minutes). Better myocardial protection, reflected by a reduction in regional myoglobin and systemic troponin I release, might be an additional mechanism for quicker recovery after the hybrid procedure.

Compared with OPCAB, patients undergoing the hybrid procedure showed a reduced transcardiac gradient of F1.2, a marker of thrombin production. This methodology has been used to assess coagulation activity within the upstream coronary circulation in a wide range of clinical studies.¹⁰⁻¹² F1.2 is a proved risk factor for thrombosis of stents¹³ or bypass grafts¹⁴ and predicts morbidity after cardiac surgery. Potential triggers for thrombin in patients undergoing OPCAB are the obligatory periods of warm ischemia¹⁵ or the grafting of the more thrombogenic SVG versus using all arterial conduits.¹⁶ Additionally, reversal of heparin with protamine, avoided in the hybrid group, is known to provoke a transient "rebound" increase in thrombin formation. As evidenced by a significant difference in postoperative ACT, the heparin effect resolved in the patients undergoing the hybrid procedure after the time point at which transcardiac F1.2 levels were analyzed. This assay might reflect changes in the kinetics of thrombin formation and not just a determination of the relative thrombogenicity of each procedure. On the other hand, the safe use of more aggressive antithrombotic therapies, such as heparin administration without reversal, is the result of less risk of bleeding after the hybrid procedure.

Undoubtedly, there are a variety of factors that influence the calculus of regional thrombin production after surgical revascularization.

A final advantage of the hybrid procedure is that it provides surgical revascularization without requiring an SVG. Although our study was not sufficiently powered to document a difference in target-vessel patency between groups, the use of the SVG is well known to limit the longevity of surgical treatment for multivessel CAD. All arterial grafting provides a theoretic advantage over the hybrid procedure by avoiding patient exposure to the potential risks of intracoronary restenosis, thrombosis, or both from either stents or SVGs. However, all-arterial grafting has not been enthusiastically adopted by most cardiac surgeons, in part because the best choice for arterial conduits after the LITA remains controversial. The right internal thoracic artery has shown excellent patency rates and increased survival advantage¹⁷⁻¹⁹ but is not often used because of the fear of sternal infection and a variety of other technical considerations.^{20,21} The radial artery is a versatile arterial conduit accustomed to pulsatile pressure but has demonstrated highly variable early patency results, preventing a consensus about its role in CABG.^{22,23} As a result, a recent review of the Society of Thoracic Surgeons database indicates that 95% of CABG cases nationwide involve an SVG. Therefore the hybrid procedure might be a more practical solution for avoiding the well-known limitations of the SVG than all-arterial grafting.

Limitations

This pilot study has limitations that need to be considered when interpreting the data. First, patient assignment to groups was nonrandomized. Although this could serve to bias the selection of lower-risk patients for the minimally invasive approach, our hybrid cohort had a higher incidence of chronic obstructive pulmonary disease, peripheral vascular disease, and prior myocardial infarction and stroke compared with the OPCAB control group.

Second, subjective measures, such as the patient's satisfaction and time to return to work, could have been influenced by preconceived notions about the superiority of the hybrid approach. However, randomization is not able to blind the patient to whether a minithoracotomy for the hybrid procedure or sternotomy for OPCAB was performed. The risk of this bias can only be controlled by comparing the hybrid group with one that is revascularized with multiple arterial grafts through a minithoracotomy.

Third, comparison of target-vessel patency between groups over the first postoperative year might not be sufficient to demonstrate the longevity advantages of bypass grafting over PCI that typically become evident only after 3 to 5 years of follow-up. These data provide reassurance, however, that the technical success of LAD grafting does not appear to be compromised by using a minimally invasive approach.

Finally, hybrid operating rooms with permanent fluoroscopic equipment are currently available at only a few centers, limiting the generalizability of our protocol. Our results cannot be extrapolated to the hybrid procedure performed as a staged procedure. Proliferation of percutaneous procedures for vascular stenting and valvular disease might make rooms for the simultaneous hybrid procedure more common in the future. Although our data support the feasibility of the hybrid approach, it is best interpreted as hypothesis generating to support the design of more appropriately powered, randomized studies in the future.

Conclusions

In conclusion, the treatment of multivessel CAD with the simultaneous hybrid approach provides a rapid recovery and a level of patient satisfaction that compares favorably with that of traditional OPCAB. These results were seen without significantly increasing costs or compromising graft patency. In addition, local activation of inflammation and coagulation was minimized by the hybrid procedure, perhaps because of reduced myocardial manipulation and warm ischemia. These promising early findings warrant further investigation of the simultaneous hybrid procedure.

References

- Diegeler A, Thiele H, Falk V, Hambrecht R, Spyridis N, Sick P, et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. *N Engl J Med*. 2002;347:561-6.
- Hueb WA, Bellotti G, de Oliveira SA, Arie S, de Albuquerque CP, Jatene AD, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol*. 1995;26:1600-5.
- Subramanian VA, McCabe JC, Geller CM. Minimally invasive direct coronary artery bypass grafting: two-year clinical experience. *Ann Thorac Surg*. 1997;64:1648-53.
- Frazier AA, Qureshi F, Read KM, Gilkeson RC, Poston RS, White CS. Coronary artery bypass grafts: assessment with multidetector CT in the early and late postoperative settings. *Radiographics*. 2005;25:881-96.
- Cohen HA, Zenati M, Smith AJC, Lee JS, Chough S, Jafar Z, et al. Feasibility of combined percutaneous transluminal angioplasty and minimally invasive direct coronary artery bypass in patients with multivessel coronary artery disease. *Circulation*. 1998;98:1048-50.
- Riess F-C, Bader R, Kremer P, Kuhn C, Kormann J, Mathey D, et al. Coronary hybrid revascularization from January 1997 to January 2001: a clinical follow-up. *Ann Thorac Surg*. 2002;73:1849-55.
- Vassiliades TA, Douglas JS, Morris DC, Block PC, Ghazzal Z, Rab ST, et al. Integrated coronary revascularization with drug-eluting stents: immediate and seven-month outcome. *J Thorac Cardiovasc Surg*. 2006;131:956-62.
- Arom KV, Emery RW, Flavin TF, Petersen RJ. Cost-effectiveness of minimally invasive coronary artery bypass surgery. *Ann Thorac Surg*. 1999;68:1562-6.
- Puskas J, Williams W, Mahoney EM, Huber PR, Block PC, Duke PG, et al. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA*. 2004;291:1841-9.
- Scharf RE, Tomer A, Marzec UM, Teirstein PS, Ruggeri ZM, Harker LA. Activation of platelets in blood perfusing angioplasty-damaged coronary arteries. Flow cytometric detection. *Arterioscler Thromb Vasc Biol*. 1992;12:1475-87.

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11. Oltrona L, Eisenberg PR, Lasala JM, Sewall DJ, Shelton ME, Winters KJ. Association of heparin-resistant thrombin activity with acute ischemic complications of coronary interventions. *Circulation*. 1996;94:2064-71.
 12. Neumann FJ, Ott I, Gawaz M, Richardt G, Holzapfel H, Jochum M, et al. Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation*. 1995;92:748-55.
 13. Neumann FJ, Gawaz M, Ott I, May A, Mossmer G, Schomig A. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. *J Am Coll Cardiol*. 1996;27:15-21.
 14. Moor E, Hamsten A, Blomback M, Herzfeld I, Wiman B, Ryden L. Haemostatic factors and inhibitors and coronary artery bypass grafting: pre-operative alterations and relations to graft occlusion. *Thromb Haemost*. 1994;72:335-42.
 15. Kon ZN, Kwon MH, Collins MJ, Kallam S, Sangrampurkar R, Ozeki T, et al. Off-pump coronary artery bypass leads to a regional hypercoagulable state not detectable using systemic markers. *Innovations*. 2006;1:232-8.
 16. Poston RS, Gu J, Brown JM, Gammie JS, White C, Nie L, et al. Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2006;131:122-30.
 17. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, et al. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855-72.
 18. Pick AW, Orszulak TA, Anderson BJ, Schaff HV. Single versus bilateral internal mammary artery grafts 10-year outcome analysis. *Ann Thorac Surg*. 1997;64:599-605.
 19. Galbut DL, Traad EA, Dorman MJ, DeWitt PL, Larsen PB, Kurlansky PA, et al. Coronary bypass grafting in the elderly. Single versus bilateral internal mammary artery grafts. *J Thorac Cardiovasc Surg*. 1993;106:128-35.
 20. Loop FD, Lytle BW, Cosgrove DM, Mahfood S, McHenry MC, Goormastic M, et al. J. Maxwell Chamberlain memorial paper. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. *Ann Thorac Surg*. 1990;49:179-87.
 21. Grossi EA, Esposito R, Harris LJ, Crooke GA, Galloway AC, Colvin SB, et al. Sternal wound infections and use of internal mammary artery grafts. *J Thorac Cardiovasc Surg*. 1991;102:342-6.
 22. Desai ND, Cohen EA, Naylor CD, Fremes SE. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med*. 2004;351:2302-9.
 23. Khot UN, Friedman DT, Pettersson G, Smedira NG, Li J, Ellis SG. Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. *Circulation*. 2004;109:2086-91.

Discussion

Dr Marc Ruel (Ottawa, Ontario, Canada). I enjoyed your presentation. I regularly perform MVST as well. I think it is a great operation. I wanted to ask you a couple of technical questions about this operation.

First, I see that most of your patients underwent 2-vessel revascularization. As you know, it is possible to do complete triple-vessel revascularization. With regard to that, how often do you bypass the right artery or its branches, and if you do a 3-vessel revascularization, what is your conduit selection strategy?

Dr Kon. Thank you. I am going to defer this question to my primary investigator.

Dr Poston. I am Robert Poston, senior author of the study and the one who did these procedures. The question of whether we incompletely revascularized our patients who underwent a minimally invasive approach is important. We do not want to emphasize the use of minithoracotomy and having the patient leave the hospital sooner more than performing an effective operation. As shown in

the slide, we actually had 2.5 diseased vessels in the MVST group, the hybrid group had 2.7, and our standard OPCAB total is 2.8. I agree with you that these patients had less total disease than you might see with a typical CABG referral that requires 3- or 4-vessel grafting. However, the minimally invasive and sternotomy groups were fairly comparable in terms of their disease. In addition, the ratio of the number of diseased to the number of revascularized vessels was also similar between groups, with only a slight reduction in the MVST group at 0.88, which was not likely to be clinically significant.

The most compelling case about choosing the minimally invasive surgery approach is the use of arterial grafts and avoiding the limitations of the vein grafts that are used in 95% of sternotomy cases. We know that vein grafts are going to fail at a higher rate both at the early time point and at rates of up to 30% at 1 year, as evidenced by the recently published PREVENT IV trial.

Dr Valavanur Subramanian (New York, NY). We presented our multivessel/small vessel thoracotomy for multiple coronary artery bypass, paving the way for outpatient surgery. Our length of stay was actually very good—less than 3 days in the majority of the patients—and about 50% went home 14 hours after the operation.

Therefore my question is this: If you are able to perform multiple arterial grafting through the MVST approach, why the hybrid procedure, except for the right coronary artery?

Dr Kon. A lot of that has to do with the right coronary artery. You are limited to the lateral anterior surface of the heart, whereas the hybrid procedure allows you to really revascularize right-sided lesions.

Dr Poston. I would echo that. It is just technically much more straightforward to put a stent in a vessel going to the posterior heart than to try to graft that. Therefore that was always our first choice, particularly with the use of a coated stent that is going to perform quite well in the long term compared with a vein graft. A case can be made that the stent might exceed the results of even the radial artery graft because you do not have to deal with conduit spasm, an issue that has not completely been resolved with the radial artery. There might even be an increased propensity to spasm when the radial artery is used as a Y graft, which is the rule for minimally invasive cases. Therefore if we had a good candidate with a stentable right or circumflex artery, but particularly for the right coronary artery, as you suggested, then the hybrid procedure was the first choice for our minimally invasive program.

Dr Michael A. Acker (Philadelphia, Pa). Rob, with the new information about the drug-eluting stents, do you still feel that way? When you put a drug-eluting stent in now, it is really an issue for life. You have all seen these acute thromboses, and it is now being recognized, even by the cardiology community, where the pendulum is swinging, because now they want to put in the bare-metal stents. They are nervous about the drug-eluting stents.

Dr Poston. It depends on the quality of the target. If you are putting coated stents into small coronary arteries, then that thrombosis issue is going to be real, but if you put it into a large proximal vessel of 3.0 mm in diameter, then it would seem that the risk of thrombosis is going to be pretty low. According to the US Food and Drug Administration's preliminary analysis, the thrombosis issue is largely related to pushing the envelope with off-label use of stents and probably not so much with the on-label use in the large coronary targets.

1007 **Dr Ralph J. Damiano** (*St Louis, Mo*). Congratulations on your
 1008 very nice presentation. You just touched briefly on the economics of
 1009 this approach. First, I would tell you that length of stay in a non-
 1010 blinded study is extremely subjective, and I would not put much em-
 1011 phasis on those data. Saving one day in the hospital really saves you
 1012 little. Most of the cost of coronary surgery is incurred in the operat-
 1013 ing room and in the first 24 hours.

1014 I would wonder whether you have done an economic analysis be-
 1015 cause your approach, I think, is expensive and is another reason
 1016 probably not to adopt this as opposed to just doing MVST or an OP-
 1017 CAB. Have you looked at the cost of this, including the cost of your
 1018 coated stent, and then have you looked at the cost of having to stay
 1019 on clopidogrel for a full year, which I am sure you tell your patients
 1020 to do. Basically, in most hospitals you have eliminated any possibil-
 1021 ity for any elective surgery for the next year. Therefore after a year of
 1022 including the clopidogrel cost in your hybrid group compared with
 1023 your other groups, could you describe the difference in the health
 1024 care economics of these approaches?

1025 **Dr Kon.** Thank you very much for that question. In fact, we did
 1026 do a cost analysis because we were worried that the additional cost
 1027 of these stents would be significant. However, primarily because
 1028 the patients stayed in the hospital a shorter period of time and
 1029 ICU time and blood transfusions were reduced, we did not see
 1030 a significant increase in costs between the hybrid procedure and
 1031 OPCAB groups.
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1035 As far as clopidogrel use over 1 year, I cannot give you numbers,
 1036 but definitely in the short term total cost of the procedure and postop-
 1037 erative hospital care was equivalent between groups, with only a minor
 1038 increase, which was not statistically significant, in the hybrid group.

1039 **Dr Michael Mack** (*Dallas, Tex*). Dr Kon, let me ask you 2 ques-
 1040 tions. I assume that these patients were not randomized, and if not,
 1041 why not?

1042 **Dr Kon.** Traditionally, patients with 2- or 3-vessel disease in our
 1043 institution underwent a standard OPCAB sternotomy. We recently
 1044 began a minimally invasive program in which we wanted to effec-
 1045 tively do a pilot study just to see how efficacious these procedures
 1046 were, and after these findings, we certainly hope to attempt a larger
 1047 randomized trial to confirm these results.

1048 **Dr Mack.** Three of your 4 end points are very caregiver driven: time
 1049 to extubation, ICU stay, and length of hospital stay. Were these all pro-
 1050 tocol-driven management issues because there is a wide variability in
 1051 anesthesiologists and preference for extubation and things like that?

1052 **Dr Kon.** It is true that specifically hospital stay and perhaps even
 1053 ICU stay are very subjective as far as the caregiver's decisions of
 1054 when to allow a patient to leave or to advise a patient to leave, but
 1055 that is why we specifically followed up with more objective analyses
 1056 that were not biased by the perception of the caregiver, such as inci-
 1057 sional pain time and time to return to work and overall satisfaction.
 1058 The actual decision to leave the ICU or hospital was based on
 1059 physician preference.
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