One-Year Coronary Bypass Graft Patency
A Randomized Comparison Between Off-Pump and On-Pump Surgery
Angiographic Results of the PRAGUE-4 Trial

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Background—Off-pump coronary bypass surgery has become a widely used technique during recent years. However, limited data are available with regard to 1-year patency of bypass grafts implanted on the beating heart in unselected consecutive bypass surgery candidates. The aim of this study was to compare 1-year angiographic patency of bypass grafts done on the beating heart (off pump) with those done classically (on pump).

Methods and Results—The PRAGUE-4 trial randomized 400 consecutive nonselected cardiac surgery candidates into group A (on pump; n=192) and group B (off pump; n=208). One-year follow-up coronary angiography was done in 255 patients. The arterial graft patency after 1 year was 91% in both groups. Saphenous graft patency was 59% (on pump) versus 49% (off pump; P<NS). Saphenous graft patency per patient was lower in the off-pump group: 0.7 patent anastomosis per patient versus 1.1 patent anastomosis in the on-pump group (P<0.01). There were 46% on-pump patients with all grafts patent versus 52% off-pump patients (P<NS). Grafts anastomosed distally to collateralized chronic total occlusions of native coronary arteries remained patent in 100% on the left anterior descending artery compared with 23% on other arteries (P<0.0001).

Conclusions—The patency of arterial coronary bypass grafts done on the beating heart is excellent and equal to grafts done on pump. The off-pump procedure in the unselected patient population results in fewer patent saphenous grafts per patient. (Circulation. 2004;110:3418-3423.)

Key Words: angiography ▪ coronary artery bypass ▪ heart ▪ surgery

The enormous progress in interventional cardiology during last 10 years has resulted in a major change in the spectrum of patients referred for coronary bypass surgery. These patients are older and sicker and frequently have had previous (multiple) percutaneous coronary interventions. Thus, cardiac surgery is competing by adding new surgical techniques: off-pump open-chest coronary bypass surgery (OPCAB), minithoracotomy bypass surgery, videothoracoscopic (robotic) procedures, etc.

Several registries published during the past 5 years have proved OPCAB to be safe and clinically effective.1–4 A few randomized studies5,6 have proved in a more scientific way that clinical outcomes of OPCAB are at least equal to those of classic techniques using cardiopulmonary bypass pump. The main advantages of OPCAB were described to be lower costs and (questionably) higher safety in high-risk/elderly patients.6–8 The present article presents a randomized comparison of 1-year angiographic patency of grafts done on pump compared with off pump.

Methods

Study Protocol

The study was one of a series of randomized clinical trials performed and coordinated at the University Hospital Vinohrady (Prague). From this series is derived the acronym PRAGUE-4. The study protocol was approved by the local ethics committee and by the Ministry of Health of the Czech Republic. It is fully described in the original article, which analyzed early surgical outcomes.9 In brief, patients were randomized to either on-pump or off-pump surgical technique by a cardiologist after indication for bypass surgery. The surgeons could not influence the randomization; ie, they were not allowed to influence the selection of patients (specifically, surgeons were not allowed to exclude from randomization patients with anatomy unsuitable for off-pump surgery). All consecutive patients with chronic coronary artery disease or unstable/postinfarction angina pectoris who signed written informed consent were randomized. Thus, the study population represents all (nonselected) real-life patients scheduled for coronary bypass surgery. The exclusion criteria were emergency surgery for ongoing myocardial ischemia, significant valvular disease, or significant aortic aneurysm (requiring surgery). One-year follow-up coronary angiography was part of the protocol.

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TABLE 1. Patient Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>On-Pump Procedure (n = 132)</th>
<th>Off-Pump Procedure (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>61.4</td>
<td>61.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Mean ejection fraction, %</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Angina pectoris, mean CCS class</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Known hyperlipidemia, %</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Mean preoperative cholesterol, mmol/L</td>
<td>5.67±0.54</td>
<td>5.72±0.49</td>
</tr>
<tr>
<td>Urgent surgery for acute coronary syndrome, %</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Elective surgery for acute coronary syndrome &gt;1 mo after episode, %</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>Single-vessel disease, n</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Double-vessel disease, n</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Triple-vessel disease, n</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Left main disease, n</td>
<td>17</td>
<td>13</td>
</tr>
</tbody>
</table>

P=NS for all.

TABLE 2. Periprocedural Data

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood loss (median), mL</td>
<td>680</td>
<td>560</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatine kinase-MB 6 h after surgery (median), μkat/L</td>
<td>0.56</td>
<td>0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation, %</td>
<td>24</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Revision (reopening of the chest), %</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Intra-aortic counterpulsation, %</td>
<td>0</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Low cardiac output syndrome, %</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Surgical Techniques

The cardiac surgical technique is described completely in the clinical article. Surgical access was through a median sternotomy in all cases, and the left internal mammary artery and great saphenous vein were harvested. In group A (on pump), cardiopulmonary bypass was established after standard ascending aorta cannulation and 2-stage venous cannulation of the right atrium. Heparin was given at a dose of 300 IU/kg to achieve an activated clotting time of 480 seconds. In all patients, normothermic perfusion with antegrade intermittent cold crystalloid cardioplegia was used. After completion of all anastomoses, protamine was given to reverse the effect of heparin. In group B (off pump), heparin was given at a dose of 100 IU/kg. Access to the anastomosis site was gained by heart elevation, initially with deep pericardial stay sutures and then with the suction Axius Xpose Device (Guidant). The Access Ultima System (Guidant) or Ultima Vacuum Assist (Guidant) device was used to stabilize the anastomosis site. Bleeding of the anastomosis site was controlled with silicone surgical tape (Quest) placed above and below the anastomosis. After the central anastomoses were performed with partial clamping, heparinization was reversed with protamine.

Surgeons

The annual workload at the study center varies between 750 and 1000 cardiac surgery procedures annually (mean of 83% coronary bypass surgery and 17% valve or aortic surgery). The center has 4 cardiac surgeons, each performing 150 to 250 cardiac procedures per year. All surgeons had experience with the off-pump technique, which was adopted in this center in 1996. For details, see the clinical article. The most important perioperative data are summarized in Table 2.

Coronary Angiograms

Preoperative and 1-year follow-up coronary angiograms were done during a 2-day hospital stay with 6F diagnostic catheters via the right femoral artery in 255 patients. Both native coronary arteries and all bypass grafts were selectively visualized in multiple projections. The mean preoperative percent diameter stenosis did not differ among different coronary arteries (left anterior descending [LAD], 87%; diagonal, 79%; left circumflex/obtuse marginal, 80%; posterolateral, 71%; right coronary artery, 83%; and left main coronary artery, 69%). For the purposes of this study, grafts were assessed as either patent or closed (because only 5 patients had patent plus diseased graft). All follow-up angiograms were done as surveillance (prescribed by the study protocol). Only 7 study patients underwent a nonscheduled coronary angiogram for symptoms during the first year. These patients did not come for surveillance angiography and thus are not part of this analysis (4 had an occluded venous graft, 1 had a graft stenosis, and 2 had all grafts patent).

Statistical Analysis

The angiographic data were analyzed on the basis of the operative technique actually used, including 28 crossovers after randomization (see Reference 9 for details). Continuous variables are presented as mean values and compared by Student’s t test. The normally distributed continuous data are presented as median values and compared by Mann-Whitney test. The percentage occurrence of certain data (eg, graft occlusion in each group) was compared by the
Results

The primary clinical end point was described in the first study report.9 For a better understanding, see Figure 1.

One-Year Patency of Grafts Done On Pump Versus Off Pump

The 1-year patency rates of arterial and saphenous grafts in both groups are shown in Figure 2. These results show that left internal mammary artery (LIMA) graft patency remains high with either surgical technique. Saphenous vein graft patency was surprisingly low with both techniques, with a trend toward better results in the on-pump group. The mean number of patent distal anastomoses decreased significantly during the first postoperative year in both groups, and the absolute number of patent anastomoses after 1 year was lower after saphenous grafts done off pump (Table 3) because of the combined effect of the fewer anastomoses done and a decrease in patency. The patency per patient did not differ significantly between groups A and B: 46% patients in group A compared with 52% in group B had all grafts patent (P=NS), 33% compared with 31% had 1 occluded graft (P=NS), and 21% compared with 17% had at least 2 grafts occluded (P=NS).

Clinical or Pharmacological Factors Possibly Influencing the Low Patency Rates

As mentioned, we were surprised by the unexpected low saphenous graft patency rates in both groups. The antithrombotic therapy was described in Methods. Detailed analysis did not show any differences in antithrombotic therapy between patients with patent and those with occluded grafts. No difference in bypass patency rates was seen between diabetics (75% overall graft patency) and nondiabetics (68% overall patency; P=NS) or between those receiving statin therapy (69% patency) and those not treated by statins (68% patency; P=NS).

Possible Angiographic Factors Influencing Patency Rates

The mean preoperative percent diameter stenosis was not different between arteries with postoperative graft occlusion (preoperative mean, 85% LAD stenosis in patients in whom the LIMA graft occluded) and arteries to which the graft remained patent (preoperative mean, 88% LAD stenosis in those in whom the LIMA remained patent; P=NS). The same was true for saphenous grafts (81% versus 79% stenosis; P=NS). The possible influence of less severe (<70%) stenoses on graft patency is shown in Figure 3. Basically, the patency did not differ significantly whether the grafted vessel had 60% or 90% stenosis. The influence of the coronary artery to which the graft was anastomosed revealed the highest patency rates for grafts anastomosed to the LAD (Table 4). There was no statistically significant difference in patency among grafts anastomosed to various other coronary arteries. The only significant angiographic predictor of future graft occlusion was preoperative chronic collateralized total coronary occlusion of an artery other than the LAD (Figure 4). Interestingly, all grafts anastomosed distally to a chronic total LAD occlusion remained patent.

Possible Clinical Implications of Graft Occlusion: CCS Classification

The mean preoperative Canadian Cardiovascular Society (CCS) class was 2.6 in group A versus 2.8 in group B

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Distal Anastomoses Done per Patient</th>
<th>Mean Distal Anastomoses Patent per Patient at 1-y CAG</th>
<th>Mean Distal Venous Graft Anastomoses Patent at 1-y CAG</th>
<th>P (vs 1-y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>2.7</td>
<td>2.0</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>2.3</td>
<td>1.6</td>
<td>0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P, group A vs B</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

CAG indicates coronary angiogram.
This classification profoundly decreased postoperatively to 0.7 in both groups \((P=\text{NS})\). There was no significant difference in the mean number of patent distal anastomoses between patients in CCS class 0 to I compared with those in class II and those in class III to IV at 1 year. The incidence of patients with clinical events (myocardial infarction, repeated revascularization, CCS class III to IV angina at 1 year) was 9.4% among patients without graft occlusions compared with 13.8% incidence among patients with at least 1 graft occluded \((P=\text{NS}, P=0.391)\). There were no instances of death or stroke between discharge from cardiac surgery and 1-year follow-up.

### Discussion

#### Off-Pump Surgery

OPCAB is now a widely used method of revascularization. Several studies have shown its feasibility and safety and provided similar results compared with classic on-pump CABG.\(^1\)\(^-\)\(^4\) The off-pump procedure may reduce the risk of perioperative complications.\(^5\)\(^-\)\(^7\) Some studies have shown lower costs associated with off-pump surgery.\(^8\)\(^-\)\(^10\) Data on graft patency after OPCAB usually show equal patency of arterial grafts (compared with on pump) and lower patency of saphenous grafts by the off-pump method.\(^11\)\(^-\)\(^12\) The early patency rates (after operation) were 96% for arterial grafts and 86% for saphenous vein grafts. One-year follow-up coronary angiogram was performed in 74% of patients, and the patency rate was 98% for arterial grafts and 68% for venous grafts.\(^20\)

#### Randomized Comparisons

A recent meta-analysis found a potential clinical benefit of OPCAB, indicating that the avoidance of extracorporeal circulation might result in improved clinical outcomes.\(^5\) A pooled analysis of 2 randomized controlled trials (BHACAS 1 and 2) showed that off-pump coronary surgery significantly lowers in-hospital morbidity without compromising outcome in the first 1 to 3 years after surgery compared with conventional on-pump coronary surgery.\(^5\) The randomized, prospective Utrecht Octopus Method Study (OCTOPUS) also evaluated bypass graft patency 1 year after operation.\(^21\)

#### On-Pump Surgery

Early patency of arterial grafts to the LAD is as high as 98% in some studies.\(^22\) The Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamol and Acenocoumarol/Phenprocoumon Study (CABADAS) trial showed occlusion rates for vein grafts 1 year after operation of 17% in women and 12% in men and occlusion rates for LIMA grafts of only 3% and 6% in women and men, respectively.\(^23\) A good harvesting technique is crucial for good long-term patency of saphenous vein grafts.\(^24\)\(^-\)\(^25\) The grafting technique used (sequential graft or single-vessel graft),\(^26\)\(^-\)\(^28\) experience of the cardiac surgeons, and perioperative to long-term antithrombotic treatment\(^29\)\(^-\)\(^35\) are important for long-term graft patency. Vessel diameter, wall motion of the supplied myocardial region, and location of the grafted vessel also determine graft patency during the first postoperative year.\(^36\) Quality and diameter of the anastomosed peripheral vessel and blood flow through the native vessel play an important role.\(^37\) The time elapsed after operation clearly influences graft patency.\(^38\) Diabetes mellitus has no influence on patency of arterial or venous grafts.\(^39\) Levels of preoperative lipoprotein(a) and homocysteine have no influence on graft patency.\(^40\) Use of statins might be associated with a lower rate of graft occlusion.\(^41\)

### Why Was the Bypass Graft Patency in This Trial Lower Than in Previous Trials?

Besides the main result (similar patency of the beating-heart grafts and classic on-pump grafts), the most surprising finding in this study was the low saphenous graft patency in both study groups. This can be explained by the fact that this study was meticulously prepared not to allow cardiac surgeon to influence patient selection for the study. Thus, this study reflects the real-life everyday practice of cardiac surgery at the beginning of the 21st century. This means that almost all

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**TABLE 4. Patency of Grafts Anastomosed to Specific Coronary Arteries**

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>91</td>
<td>91</td>
<td>NS</td>
</tr>
<tr>
<td>D</td>
<td>73</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>LCx/OM</td>
<td>56</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>PL</td>
<td>55</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>60</td>
<td>52</td>
<td>NS</td>
</tr>
</tbody>
</table>

D indicates diagonal; LCx/OM, left circumflex/obtuse marginal; PL, posterolateral; and RCA, right coronary artery.
patients with good-quality vessels (ie, vessels >2 mm, without heavy diffuse calcifications, without chronic total occlusions) are treated by percutaneous coronary interventions. Thus, the current cardiac surgery patient population consists of patients not suitable for angioplasty—the most advanced coronary artery disease cases. Most of the older trials investigating angiographic bypass graft patency after classic on-pump surgery were done 10 to 20 years ago, well before the modern stent era. Thus, they enrolled patients with entirely different (ie, better) coronary arteries. The more recent off-pump registries or even randomized trials\(^2\) comparing off-pump and on-pump procedures are limited by patient preselection by the surgeon; these registries and trials enrolled only those patients who were considered suitable for the off-pump procedure. Thus, they excluded patients with early postinfarction (<3 months),\(^2\) severe left ventricular dysfunctions,\(^2\) small (<2 mm) and diffusely diseased/calcified coronary arteries, etc. The patency rates therefore were higher than in our study. Furthermore, there is a potential bias toward decreased bypass graft patency in this angiographic follow-up study: 127 patients (33% of all patients who were discharged alive from cardiac surgery) did not come for the follow-up angiography, mostly because they were completely symptom free. It may well be that these patients had fewer bypass occlusions than the 255 patients undergoing follow-up angiography.

Thus, the 1-year arterial graft patency was high with both the off-pump and on-pump surgical techniques. Saphenous graft occluded frequently during the first year with both techniques, possibly reflecting the current spectrum of cardiac surgery candidates: patients with very diffuse disease (and thus poor distal runoff) not amenable to percutaneous intervention. The lowest patency rates were among grafts anastomosed on collateralized totally occluded coronary arteries other than the LAD. The number of patent venous grafts 1 year after beating-heart surgery is lower compared with classic surgery.

**Acknowledgments**

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