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Intraoperative Fluorescence Imaging System for On-Site Assessment of Off-Pump Coronary Artery Bypass Graft

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Stanford, California; and Hiratsuka, Japan

OBJECTIVES The aim of this study was to evaluate the intraoperative fluorescence imaging (IFI) system in the real-time assessment of graft patency during off-pump coronary artery bypass graft.

BACKGROUND Intraoperative fluorescence imaging is an intraoperative angiography-like imaging modality using fluorescent indocyanine green excited with laser light. Recently, assessment of graft patency using the IFI system was introduced into clinical use. The feasibility and efficacy of IFI technology in off-pump coronary artery bypass graft has not been systematically compared with other conventional diagnostic modalities.

METHODS Patients undergoing off-pump coronary artery bypass graft received IFI analysis, intraoperative transit time flowmetry, and postoperative X-ray angiography. In off-line IFI analysis, the graft washout was classified based on the number of heartbeats required for indocyanine green washout: fast washout (≤15 beats) and slow washout (>15 beats).

RESULTS A total of 507 grafts in 137 patients received IFI analysis. Of all the IFI analyses, 379 (75%) grafts were visualized clearly up to the distal anastomosis. With regard to anastomosis location, anterior location was associated with a higher percentage of fully analyzable images (90%). More than 80% of images were analyzable, irrespective of graft type. Six grafts with acceptable transit time flowmetry results were diagnosed with graft failure by IFI, which required on-site graft revision. All revised grafts' patency was confirmed by post-operative X-ray angiography. Conversely, 21 grafts with unsatisfactory transit time flowmetry results demonstrated acceptable patency with IFI. Graft revision was considered unnecessary in these grafts, and 20 grafts (95%) were patent by post-operative X-ray angiography. Compared with slow washout, fast washout was associated with a higher preoperative ejection fraction, use of internal mammary artery grafts, and anterior anastomosis location.

CONCLUSIONS The IFI system enables on-site assessment of graft patency, providing both morphologic and functional information. This technique may help reduce procedure-related, early graft failures in off-pump bypass patients. (J Am Coll Cardiol Img 2009;2:604–12) © 2009 by the American College of Cardiology Foundation
Compared with conventional on-pump coronary artery bypass graft (CABG) surgery, off-pump CABG potentially decreases the incidence of myocardial injury, renal damage, and central nervous system complications (1–4). However, the clinical benefits of off-pump CABG are partly offset by a mildly higher rate of early graft occlusion (1). Several diagnostic measures including transit time flowmetry (TTFM) have been used for intraoperative assessment of graft patency. However, their efficacy is limited due to the lack of standardized criteria and/or lack of clear visualization of anastomoses.

**METHODS**

**Study design and patients.** All patients undergoing off-pump CABG between January 2002 and May 2005 at Hiratsuka Kyosai Hospital (Hiratsuka, Japan) received IFI assessment and compose the study population.

A portion of patients underwent minimally invasive direct coronary artery bypass graft (MID-CABG), defined as off-pump surgery without sternotomy. Exclusion criteria included patients with known history of iodine allergy, and patients who subsequently required on-pump CABG. All medications were prescribed as clinically indicated. The protocol was approved by the ethical committee, and all patients gave written informed consent to participate in this study.

**IFI system.** The IFI system (Novadaq Technologies Inc., Concord, Ontario) used for image acquisition has been previously described (5,7). In summary, the imaging device depends on the fluorescence properties of ICG dye when illuminated by a near-infrared laser light source. After injection of diluted ICG (0.625 mg in 0.5 ml saline) through a central venous catheter, ICG is rapidly flushed with 10 ml of normal saline. The fluorescence sequentially shows illumination of the graft and coronary artery lumen, perfusion territory, and coronary vein

To compare IFI with angiography, the quality of images obtained was classified as follows: 1) fully analyzable: clear and full visualization of graft, distal anastomosis and native coronary; and 2) partially analyzable: clear visualization of graft body with poor or no visualization of distal anastomosis, and/or significant arrhythmia at the time of image acquisition. The washout of ICG was visually defined as follows: fast washout (heartbeats required for ICG washout: ≤15 beats), slow washout (heartbeats required for ICG washout: >15 beats), and no-flow (ICG pooling in graft or no ICG in graft). All IFI results were analyzed by an analyst blinded to other angiographic and clinical results.

**Transit time flowmetry.** Mean graft flow (MGF) and pulsatility index (PI) were obtained using a TTFM system (Medi-Stim Butterfly Flowmeter, Medi-Stim ASA, Oslo, Norway). Mean graft flow was expressed as milliliters per minute, and PI was defined as the difference between maximum and minimum flow divided by the mean flow. In this study, unsatisfactory graft flow based on TTFM results was defined MGF ≤5 or PI >5 (11).
Quantitative coronary angiography. All conventional X-ray angiograms were assessed using an off-line quantitative coronary angiography system (Quant32, Sanders Data Systems, Palo Alto, California) by 2 experienced angiographers at the Stanford Core Cardiovascular Analysis Laboratory. Percent diameter stenosis was measured at the anastomosis with graft body as the reference. Angiographically significant lesions were defined as 50% diameter stenosis, and grafts without a significant stenosis were considered patent.

Statistical analysis. Statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, North Carolina). Continuous variables are expressed as mean ± SD, and their comparisons were performed with 2-tailed, unpaired t tests. Categorical variables were compared using chi-square or the Fisher exact test. The Fisher exact test was used if there was an expected cell value <5. Significance was assumed at a value of p < 0.05. The assessment was based on the graft as the unit of analysis, and no correction was made for the use of multiple correlated observations within patients.

RESULTS

Patient population. Intraoperative fluorescence imaging was initially attempted in a total of 507 grafts in 137 patients undergoing off-pump CABG. Baseline patient characteristics are shown in Table 1. Acute coronary syndrome comprised 39% of the patients. Postoperative angiography was performed 13.5 ± 6.3 days after surgery. In this series, 18% of the patients received MID-CABG.

Image acquisition was unavailable in 37 grafts (7%) due to unstable hemodynamic condition and/or anatomical position of the grafts. Another 91 grafts (18%) were classified as partially analyzable due to failure to visualize the distal anastomosis (n = 74) or significant arrhythmia (n = 17), which deemed the remaining 379 grafts (75%) fully ana-
lyzable (74% were CABG with sternotomy, and 85% were MID-CABG). Fourteen patients declined post-operative coronary angiography, resulting in 289 grafts from 116 patients eligible for complete comparison with TTFM and quantitative coronary angiography (Fig. 2).

Graft types and anastomosis location are summarized in Table 2. With regard to anastomosis location, anterior location was associated with a higher percentage of fully analyzable images. More than 80% of images were analyzable, irrespective of graft type (Fig. 3).

**Comparison among IFI, TTFM, and post-operative angiography.** A total of 289 grafts were available for comparison among IFI, TTFM, and quantitative coronary angiography. Six grafts with acceptable TTFM results (MGF >5 ml/min and PI ≤5) were diagnosed with graft failure by the IFI system, which resulted in on-site graft revision (Fig. 4, Table 3). Graft patency was confirmed with postoperative angiography in all of the 6 grafts (Fig. 5, Online Videos 2 and 3). Conversely, 21 grafts with unsatisfactory TTFM results demonstrated acceptable patency with the IFI system. Graft revision was considered unnecessary in these 21 grafts, among which 20 grafts were patent by postoperative angiography (Fig. 4). Nine grafts (11 anastomoses) out of 379 grafts were occluded at the time of postoperative angiography despite acceptable IFI results. Clinical and procedural characteristics are summarized in Table 4. Patients with a failed graft that supposedly perfused a small territory of myocardium were followed medically without further intervention.

**Angiographic result of incomplete IFI cases.** Postoperative angiographic results were partially available for the grafts that we excluded from the final analyses. Among 37 grafts whose IFI was not obtained (Fig. 2), 26 grafts received angiographic screening, confirming their patency. Similarly, among 91 grafts whose IFI were deemed as partial analysis (Fig. 2), 64 grafts received postoperative angiography, revealing 1 total occlusion.

**ICG washout.** Compared with slow washout, fast washout of the ICG was associated with a higher preoperative ejection fraction, use of internal mammary artery grafts, and anterior anastomosis loca-

**Table 2. Anatomosis Location and Graft Type**

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 507 Grafts)</th>
<th>CABG With Sternotomy (n = 468 Grafts)</th>
<th>MID-CABG (n = 39 Grafts)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal anastomosis location, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anterior</td>
<td>28</td>
<td>25</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>37</td>
<td>38</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>26</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>9</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Graft type, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IMA</td>
<td>37</td>
<td>37</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>38</td>
<td>41</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>SVG</td>
<td>22</td>
<td>20</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>GEA</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*Coronary artery bypass graft with sternotomy versus minimally invasive direct coronary artery bypass graft.

GEA = gastroepiploic artery graft; IMA = internal mammary artery graft; RA = radial artery graft; SVG = saphenous vein graft.
Figure 3. Quality of Fluorescence Image

Quality of fluorescence image was classified in 3 categories: fully, partially, and not analyzable. With regard to anastomosis location, anterior location was associated with a higher percentage of fully analyzable images. More than 80% of images were analyzable, irrespective of graft type. In a portion of patients, IFI was not obtained due to patient condition and/or anatomical graft location. GEA = gastroepiploic artery graft; RA = radial artery graft; SVG = saphenous vein graft; other abbreviation as in Figure 1.

Figure 4. Graft Revision Following IFI

A total of 289 grafts were available for comparison among IFI, TTFM, and quantitative coronary angiography. Six grafts with acceptable TTFM results (MGF >5 ml/min and PI ≤5) required revision, and graft patency was confirmed with post-operative angiography in all of the 6 grafts. Conversely, 21 grafts with unsatisfactory TTFM results showed acceptable graft patency by IFI. Graft revision was considered unnecessary in these 21 grafts, among which 20 grafts were patent by postoperative angiography. IFI = intraoperative fluorescence imaging; MGF = mean graft flow (ml/min); PI = pulsatility index; other abbreviation as in Figure 2.
tion. In comparison with quantitative coronary angiographic diameter stenosis at the anastomosis, mean percent diameter stenosis was not significantly different between the fast and slow washout groups. Mean graft flow measured by TTFM showed considerable variation in graft flow (range 2 to 161 ml/min), with no significant difference between the 2 groups (Table 5).

**DISCUSSION**

The results of this study are: 1) the IFI system was feasible in off-pump CABG, including MID-CABG; 2) there was some discrepancy between IFI and TTFM, but the IFI system was mostly in agreement with post-operative angiography; 3) post-operative angiography identified more graft failure than IFI; and 4) semiquantitative analysis of the IFI system may provide functional information on the grafts. Although the safety and feasibility of the IFI system has been previously shown (12), the present study is the first to comprehensively compare the results of the IFI system with TTFM and post-operative coronary angiography in patients undergoing off-pump CABG.

**Table 3. Findings of Graft Revision (n = 268 Grafts)**

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Number of Diseased Vessels</th>
<th>Ejection Fraction (%)</th>
<th>Graft Type</th>
<th>Distal Anastomosis</th>
<th>TTFM Assessment (MGF/PI) Before Revision</th>
<th>IFI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89</td>
<td>F</td>
<td>3</td>
<td>74</td>
<td>LIMA</td>
<td>Diagonal branch</td>
<td>Acceptable (12/2.6)</td>
<td>Occluded at distal anastomosis of LAD</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>M</td>
<td>3</td>
<td>NA</td>
<td>GEA</td>
<td>PDA</td>
<td>Acceptable (10/4.1)</td>
<td>Slow flow</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>M</td>
<td>3</td>
<td>69</td>
<td>RA</td>
<td>Diagonal branch</td>
<td>Acceptable (23/2.6)</td>
<td>Occluded at distal anastomosis of LAD</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>2</td>
<td>49</td>
<td>LIMA</td>
<td>LAD</td>
<td>Acceptable (20/2.8)</td>
<td>Slow flow</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>3</td>
<td>NA</td>
<td>LIMA</td>
<td>LAD</td>
<td>Acceptable (27/2.9)</td>
<td>Slow flow</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>M</td>
<td>3</td>
<td>85</td>
<td>LIMA</td>
<td>LAD</td>
<td>Acceptable (29/2.2)</td>
<td>Graft dissection</td>
</tr>
</tbody>
</table>

LAD = left anterior descending artery; LIMA = left internal mammary artery; PDA = posterior descending artery; other abbreviations as in Table 2.

**Figure 5. Case Example: IMA Occlusion Detected by IFI**

(A) Intraoperative fluorescence imaging before revision. Transit time flowmetry showed mean flow 22 ml/min with PI of 2.3, which was considered acceptable. However, IFI showed occlusion of IMA between diagonal branch and LAD. Also see Online Video 2. (B) Intraoperative fluorescence imaging after revision. Although TTFM did not change significantly (mean flow: 22 ml/min, PI: 2.4), IFI showed patency of IMA between diagonal branch and LAD. Also see Online Video 3. Abbreviations as in Figures 1-4.

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Recent advances in surgical techniques and devices have made off-pump CABG a feasible technique. Primarily due to its relatively lower periprocedural complication rate, off-pump CABG is becoming a preferred method in higher-risk patient subsets, including the elderly, and patients with comorbidities such as renal dysfunction (13–16). However, the benefit of off-pump CABG is partially counteracted by a slightly higher rate of early graft occlusion (1). The cause of early graft failure is multifactorial; however, procedural factors including distal graft anastomosis presumably play a central role in the majority of cases (17).

Several techniques are currently available for intraoperative graft patency assessment. Currently, TTFM, based on Doppler signals, is the most commonly used method. Although high MGF and low PI value in TTFM suggest acceptable graft patency, low MGF and higher PI do not necessarily represent poor graft anastomosis (11). Other techniques such as epicardial echocardiography and thermal coronary angiography are under development; however, their low resolution and poor accessibility to lateral or posterior walls make these technologies fall slightly short of requirements for clinical use (18–20).

In the present study, 93% of the 507 grafts in 137 consecutive off-pump patients were visualized by the IFI system. In addition, complete analysis up to the distal anastomosis was possible in 75% of grafts. The rate of successful visualization was comparable, regardless of graft type or location. Even in MID-CABG patients, images provided by the IFI system were comparable to those of off-pump CABG with sternotomy.

With its angiographic-like image, the IFI system provides direct visualization of intraoperative graft patency, enabling on-site decision for potential graft revision. In our study, 6 graft failures that required on-site graft revision were detected. All revised grafts were confirmed patent with

![Table 4. Subacute Occlusions (n = 379 Grafts in 130 Patients)](image)

![Table 5. Comparison Between Fast and Slow ICG Washout](image)
post-operative coronary angiography, which further validates the utility of IFI for intraoperative graft failure detection. Furthermore, this study demonstrated the potential of the IFI system to decrease unnecessary graft revision. In our series, 21 grafts showed acceptable patency with IFI, but their TTFM showed suboptimal flow results. A recent report demonstrated 3.8% of bypass grafts showed acceptable IFI flow despite unsatisfactory TTFM measurements (11). In our study, post-operative angiography in these grafts confirmed a patency rate comparable to the entire study cohort, validating the important role of the IFI system.

However, graft patency assessment using IFI was not in perfect agreement with those of postoperative angiography. Nine grafts were found to be occluded at the time of postoperative angiography, but the IFI system revealed acceptable intraoperative graft patency. This raises the difficult question of whether graft failure in these cases was mainly due to intraoperative issues. Possible reasons for individual subacute graft occlusion may include postoperative edema at the anastomotic site, graft kinking due to long graft, and competitive coronary flow from native coronary artery; however, the reason for subacute occlusions was not completely apparent. In some grafts, relatively small perfusion area was considered to be one of the reasons for subacute occlusion. Our study suggests that perioperative factors should be recognized as another important determinant of graft patency. This observation needs additional assessment; therefore, use of the IFI system may help to identify factors for further improvement of graft patency during off-pump CABG.

The semiquantitative analysis of the contrast dye washout showed that more rapid elimination of ICG was associated with higher ejection fraction and anterior internal mammary artery grafts. Although angiography requires forced contrast medium injection through the coronary arteries, the IFI system observes natural flow of both native vessels and grafts in off-pump CABG. The IFI washout analysis can potentially provide additional functional information that is different from blush score or frame counts by angiography. In this series, there were virtually no cases of severe graft stenosis except for several total occlusions. Thus, we are unable to assess the possible relationship of graft stenosis and ICG washout. Further analysis may be necessary to clarify the clinical implications of this IFI finding.

Study limitations. There are several limitations in this study. First, this is a pilot study from a single-center experience, which potentially limits the generalizability of findings. Second, this was not a randomized study and the decision to revise the grafts was based on IFI results. Therefore, we were unable to calculate sensitivity and specificity of the IFI system. Third, the results of the IFI system were only semiquantitatively analyzed due to lack of brightness standardization. Fourth, in this case series, grafts were fully skeletonized for better visualization by the IFI system. Incomplete skeletonization or pedicled conduits may interfere with image acquisition.

CONCLUSIONS

The IFI system enables on-site assessment of graft patency, providing both morphologic and functional information in off-pump bypass patients. This unique technique may help identify procedure-related early graft failures, permitting on-site revision, and thereby contributing to improved clinical outcomes for off-pump CABG patients.

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