Transient Ischemia Does Not Limit Subsequent Ischemic Regional Dysfunction in Humans: A Transesophageal Echocardiographic Study During Minimally Invasive Coronary Artery Bypass Surgery

MICHAEL J. MALKOWSKI, MD, FACC, CHRISTOPHER M. KRAMER, MD, FACC, SEYED TAHER PARVIZI, MD, FACC, SINDA DIANZUMBA, MD, JOSE MARQUEZ, MD, NATHANIEL REICHEK, MD, FACC, JAMES A. MAGOVERN, MD, FACC

Pittsburgh, Pennsylvania

Objectives. This study sought to assess the effects of sequential coronary artery occlusion during minimally invasive coronary artery bypass graft surgery (CABG) on hemodynamic variables and left ventricular systolic function by means of transesophageal echocardiography (TEE).

Background. Clinical and experimental studies suggest a protective effect of ischemic preconditioning in patients with acute coronary syndromes. However, the effect of repetitive myocardial ischemia on myocardial mechanical function in humans is not completely understood.

Methods. Seventeen patients with left anterior descending coronary artery (LAD) stenosis ≥70% and normal rest left ventricular systolic function referred for minimally invasive CABG underwent intraoperative TEE for assessment of regional left ventricular wall motion and measurement of hemodynamic variables at baseline (baseline 1), during a 5-min coronary occlusion (occlusion 1), after a 5-min reperfusion period (baseline 2) and a during a second coronary occlusion during bypass anastomosis (occlusion 2).

Results. Left ventricular wall motion score (LVWMS) increased significantly from baseline (16.0) to occlusion 1 (21.4 ± 3.1 [mean ± SD], p < 0.05) and occlusion 2 (21.8 ± 3.1, p < 0.05). No difference in LVWMS was noted between occlusions 1 and 2. Pulmonary artery systolic pressure increased significantly from baseline (25 ± 6 mm Hg) to occlusion 1 (32 ± 7 mm Hg, p < 0.05) and occlusion 2 (33 ± 6 mm Hg, p < 0.05). Pulmonary artery diastolic pressure also increased significantly from baseline (12 ± 4 mm Hg) to occlusion 1 (16 ± 4 mm Hg, p < 0.05) and occlusion 2 (16 ± 4 mm Hg, p < 0.05). No significant differences in pulmonary artery pressures were noted between occlusions 1 and 2.

Conclusions. Ischemic dysfunction was precipitated by the 5-min LAD occlusion, as shown by the increase in LVWMS and pulmonary artery pressure. However, a 5-min coronary occlusion and the resulting ischemia do not alter regional left ventricular systolic function during subsequent ischemia in humans.

(J Am Coll Cardiol 1998;31:1035–9)
©1998 by the American College of Cardiology

Experimental animal models support ischemic preconditioning as a mechanism that limits myocardial necrosis resulting from coronary occlusion (1–4). Thus, ischemic preconditioning may account for the clinical observations relating to preinfarction angina and smaller infarct size in acute coronary syndromes (5–8). In addition, ischemia has been reported to diminish during repeated occlusions in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) (9–13). However, the effect of repetitive ischemia on myocardial mechanical function in humans is not well understood (9,14).

Minimally invasive coronary artery bypass graft surgery (CABG) involves bypassing a coronary artery under direct visualization (15). The procedure avoids cardiopulmonary bypass, and the anastomosis is performed on a beating heart while the recipient vessel is occluded. A brief test occlusion is often done and released before the anastomosis. Intraoperative transesophageal echocardiography (TEE) during minimally invasive CABG provides a unique opportunity to study the effects of coronary occlusion on myocardial function. We hypothesized that the extent and severity of regional dysfunction during occlusion for anastomosis would decrease after a 5-min test occlusion. Thus, the present study reports the effects of sequential coronary occlusion on hemodynamic variables and left ventricular regional function as assessed by TEE during minimally invasive CABG.

Methods

Study group. Twenty-three patients referred for minimally invasive CABG of the left anterior descending coronary artery
between March 1, 1996 and August 15, 1996 were evaluated for the study. All patients had significant intraluminal obstruction (>70%) of the LAD by coronary angiography. In addition, all patients underwent intraoperative TEE as part of the minimally invasive CABG procedure and were assessed for the development of segmental wall motion abnormalities in the anterior or apical regions, or both, during an intraoperative preliminary 5-min LAD occlusion. Six patients were excluded from the study. Three patients had baseline akinesia or hypokinesia in the LAD territory or 70% right coronary artery stenosis (n = 2), or both, and three patients did not display regional dysfunction during the initial coronary occlusion, leaving 17 patients for analysis (Table 1).

**Minimally invasive CABG.** The operation was performed through a 6- to 8-cm left submammary incision. The fourth costal cartilage was removed, providing direct access to the left internal mammary artery (LIMA) and avoiding the need for rib spreading. The LIMA was mobilized under direct vision from the first to fifth rib with the help of a mechanical retractor to lift the third rib. Heparin (5,000 U) was given intravenously before dividing the distal end of the LIMA pedicle. The pericardium was opened and pulled up to the chest wall with sutures. The middle portion of the LAD was identified and uncovered for a distance of 2 to 3 cm. The vessel was encircled proximally and distally with Silastic loops mounted on a blunt needle. A 5-min test occlusion followed by a 5-min period of reperfusion was performed in each patient to determine the degree of hemodynamic disturbance caused by coronary occlusion and to serve as a potential means of ischemic preconditioning. The LAD was opened using a standard coronary scalpel and scissors, and the anastomosis was achieved with a running 7-0 polypropylene suture. Intercostal rib blocks with 0.25% bupivacaine were given to each patient to provide immediate pain control, which allowed extubation in the operating room immediately after wound closure.

**Echocardiography.** Intraoperative TEE was performed in all patients. The left ventricle was imaged from the transesophageal four-chamber, two-chamber and long-axis views and the transgastric short-axis and long-axis views (16). Baseline imaging was performed after induction of anesthesia but before the initial incision. Imaging was also performed during the 5-min coronary occlusion (occlusion 1), after the 5-min reperfusion period (baseline 2), during the 10 to 12 min anastomosis period (occlusion 2) and after graft anastomosis (recovery). Images were obtained during the last 2 min of occlusion 1. The transesophageal four-chamber, two-chamber and long-axis views were obtained in sequence and were followed by the transgastric short- and long-axis views. Imaging for occlusion 2 started 3 min into the stage utilizing the identical sequence used during occlusion 1, followed by continuous imaging in the view or views showing the greatest regional dysfunction. Left ventricular regional wall motion was evaluated by two investigators (H.J.M., C.M.K.) who had no knowledge of the clinical

<table>
<thead>
<tr>
<th>Pt No./ Gender</th>
<th>Age (yr)</th>
<th>LAD(% stenosis)</th>
<th>Collateral Channels Present</th>
<th>LVEF (%)</th>
<th>LVWMS BL</th>
<th>LVWMS Ocl 1</th>
<th>LVWMS Ocl 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>58</td>
<td>100</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>2/M</td>
<td>73</td>
<td>95</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>3/M</td>
<td>47</td>
<td>95</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>4/M</td>
<td>72</td>
<td>90</td>
<td>No</td>
<td>65</td>
<td>16</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>5/M</td>
<td>73</td>
<td>70</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>6/M</td>
<td>65</td>
<td>85</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>7/F</td>
<td>60</td>
<td>95</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>8/M</td>
<td>70</td>
<td>80</td>
<td>No</td>
<td>65</td>
<td>16</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>9/M</td>
<td>56</td>
<td>100</td>
<td>No</td>
<td>65</td>
<td>16</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>10/M</td>
<td>61</td>
<td>100</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>11/M</td>
<td>79</td>
<td>95</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>12/M</td>
<td>51</td>
<td>95</td>
<td>Yes</td>
<td>55</td>
<td>16</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>13/M</td>
<td>76</td>
<td>80</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>14/F</td>
<td>72</td>
<td>90</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>15/F</td>
<td>73</td>
<td>90</td>
<td>No</td>
<td>55</td>
<td>16</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>16/F</td>
<td>47</td>
<td>95</td>
<td>Yes</td>
<td>60</td>
<td>16</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>17/F</td>
<td>80</td>
<td>80</td>
<td>No</td>
<td>60</td>
<td>16</td>
<td>18</td>
<td>19</td>
</tr>
</tbody>
</table>

Mean ± SD 64 ± 11 90 ± 8 59 ± 4 16 ± 0 21.4 ± 3.1 21.8 ± 3.1

F = female; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction at baseline (BL); LVWMS = left ventricular wall motion score; M = male; Ocl 1 = occlusion 1; Ocl 2 = occlusion 2; Pt = patient.
information and stage of procedure. Utilizing the 16-segment model, regional wall motion was indexed (1 = normal; 2 = hypokinesia; 3 = akinesia; and 4 = dyskinesia), as previously described (17). A left ventricular wall motion score (LVWMS) was calculated by adding the regional index from the 16 segments for each occlusion. In addition, a baseline qualitative left ventricular ejection fraction was reported as previously described (17). Interobserver variability was minimal for the LVWMS ($r = 0.98, p < 0.0001$). Disagreement in the left ventricular wall motion index (LVWMI) was present in 2% of the segments analyzed. Disagreements regarding the LVWMS and the LVWMI were resolved with a third experienced reader (S.T.P.) by consensus.

**Hemodynamic variables.** Intraoperative hemodynamic variables were recorded at each stage of the procedure. Baseline 1, occlusion 1 and occlusion 2 pressures were compared because baseline 2 pressures were not consistently recorded. Systolic and diastolic blood pressures were obtained from an arterial catheter. Pulmonary artery systolic and diastolic pressures were obtained from a pulmonary artery catheter that was placed preoperatively in the operating suite.

**Statistical analysis.** The Friedman repeated measures analysis of variance on ranks was used to assess statistical significance of changes in LVWMS, LVWMI and pulmonary artery pressures. Post hoc multiple pairwise comparisons were provided by the Student-Newman-Keuls test. Differences in regional LVWMI between occlusion 1 and occlusion 2 stages were evaluated with the Wilcoxon signed rank test. A $p$ value $\leq 0.05$ was considered statistically significant.

**Results**

**Patient characteristics.** The study included 17 patients (12 men, 5 women; mean age 64 ± 11 years) who underwent minimally invasive CABG (Table 1). The percent LAD stenosis ranged from 70% to 100% (mean stenosis 90 ± 8%). Angiographic collateral channels were present in two patients. Baseline left ventricular ejection fraction by echocardiography was 59 ± 4%. Nine patients presented with stable and eight with unstable angina.

**Echocardiographic findings.** LVWMS was significantly different ($p \leq 0.001$) among the four stages and was significantly higher during occlusion 1 than during baseline 1 (16.0 ± 0 vs. 21.4 ± 3.1, $p < 0.05$). After reperfusion in which left ventricular function returned to normal (baseline 2), there was a statistically significant increase in LVWMS after occlusion 2 (16.0 ± 0 vs. 21.8 ± 3.1, $p < 0.05$). No significant change was observed between occlusions 1 and 2 (16.0 ± 0). Dysfunction was observed in the midanterior region in 65% of patients during occlusions 1 and 2, with a statistically significant increase in LVWMI from baselines 1 and 2 (1.0) to occlusions 1 (1.8 ± 0.9, $p < 0.05$) and 2 (1.8 ± 0.9, $p < 0.05$).

**Figure 1.** LVWMS at baseline 1, occlusion 1, baseline 2 and occlusion 2. LVWMS was significantly different ($p \leq 0.001$) among the four stages. By pairwise multiple comparison procedures, there were significant differences between baseline 1 and occlusion 1 ($p < 0.05$) and between baseline 2 and occlusion 2 ($p < 0.05$). No significant change was observed between occlusions 1 and 2. *$p < 0.05$ versus baseline 1. †$p < 0.05$ versus baseline 2.

**Figure 2.** LVWMI at baseline 1, occlusion 1, baseline 2 and occlusion 2. Statistically significant differences ($p \leq 0.001$) were observed in LVWMI among the four stages for the anteroapical (solid bars), apicoseptal (gray bars), midanteroseptal (open bars) and midanterior (hatched bars) regions. By pairwise multiple comparison procedures, there were statistically significant differences ($p < 0.05$) between baseline 1 and occlusion 1 and between baseline 2 and occlusion 2. No significant change was observed between occlusions 1 and 2 in these regions. *$p < 0.05$ versus baseline 1. †$p < 0.05$ versus baseline 2.
Similarly, dysfunction was observed in the midanteroseptal region in 41% of patients during occlusions 1 and 2, with a statistically significant increase in LVWMI from 1.0 at baseline 1 and 2 to 1.8 ± 1.0 (p < 0.05) at occlusions 1 and 2. However, there were no significant differences in LVWMI between occlusions 1 and 2.

**Hemodynamic variables.** Pulmonary systolic pressure increased significantly from baseline (25 ± 6 mm Hg) to occlusion 1 (32 ± 7 mm Hg, p < 0.05) and occlusion 2 (33 ± 6 mm Hg, p < 0.05). Pulmonary diastolic pressure also increased significantly from baseline (12 ± 4 mm Hg) to occlusion 1 (16 ± 4 mm Hg, p < 0.05) and occlusion 2 (16 ± 4 mm Hg, p < 0.05). No significant change in pulmonary artery pressure was noted between occlusions 1 and 2.

Systolic blood pressure did not change significantly from baseline (120 ± 9 mm Hg) to occlusion 1 (115 ± 10 mm Hg) or occlusion 2 (116 ± 10 mm Hg). Diastolic blood pressure did not change from baseline (65 ± 8 mm Hg) to occlusion 1 (64 ± 8 mm Hg) or occlusion 2 (65 ± 7 mm Hg).

**Discussion**

Despite the precipitation of ischemia shown by the development of left ventricular regional dysfunction and an increase in pulmonary artery pressure, the 5-min preliminary occlusion of the LAD during minimally invasive CABG did not prevent the development of ischemic regional systolic dysfunction or pulmonary artery hypertension during a subsequent occlusion. Our intraoperative TEE results are in agreement with previous echocardiographic reports that sequential coronary artery occlusion during coronary angioplasty does not result in left ventricular regional dysfunction during subsequent occlusions (14). These data do not detract from the previous observation that preinfarction angina results in less mortality in patients who develop acute coronary syndromes (5–7): rather, they indicate that the extent of systolic dysfunction does not change significantly after repeated episodes of ischemia.

**Preconditioning in clinical cardiology: comparison with published reports.** Angina preceding an acute myocardial infarction or acute coronary syndrome has been shown (5–7) to have protective effects for patients with coronary artery disease. Preinfarction angina or angina of increased frequency before a clinical event appears to result in a smaller myocardial infarction, as measured by creatine kinase elevation, fewer Q wave infarctions, less congestive heart failure, lower mortality and a greater likelihood of successful thrombolysis (5–7,18,19). One mechanism proposed for this protective effect is ischemic preconditioning. Preconditioning is thought to occur as the result of a metabolic alteration precipitated by brief episodes of ischemia that have energy-sparing effects, resulting in reduced infarct size after total occlusion. This phenomenon has been demonstrated in multiple experimental models (1–4).

Clinical studies have attempted to demonstrate cardioprotective effects of preconditioning in humans (9–13,14). Studies utilizing sequential PTCA have examined whether sequential arterial occlusions result in less myocardial ischemia, with conflicting results. Deutsch et al. (9) examined 12 patients who underwent angioplasty of the LAD and reported less electrocardiographic (ECG), hemodynamic and metabolic (myocardial lactate production) changes on subsequent coronary occlusions of ±90 s. A recent study (15) also demonstrated less ischemia by intracoronary and surface ECGs with sequential occlusion of the LAD by PTCA and after pretreatment with intracoronary adenosine. However, left ventricular wall motion was not evaluated in these studies.

The findings of the present study are in agreement with the findings of Dupouy et al. (14) who reported that brief periods of ischemia from occlusion of the LAD by means of balloon angioplasty did not protect against subsequent regional ventricular dysfunction as assessed by M-mode transthoracic echocardiography. In addition, hemodynamic variables of ischemia, including left ventricular end-diastolic pressure, showed similar increases with subsequent balloon inflations. Additional studies that assessed the effect of beta-blockade during coronary occlusion did not describe less ischemia as assessed by ECG, hemodynamic and clinical variables with subsequent occlusions before the administration of the anti-ischemic drug (20,21). Finally, Hauser et al. (22) showed that the time to regional dysfunction as assessed by echocardiography during coronary angioplasty did not decrease with sequential angioplasty balloon inflations.

One potential explanation for differences in the results of the current study and clinical observations that infarct size is limited by preinfarction angina may be related to physiologic differences between ischemic myocardial dysfunction and infarction as they relate to preconditioning. Ours was a study of transient brief ischemia, not infarction. The regional dysfunction created by the coronary occlusion during minimally invasive CABG completely resolves after revascularization. It is possible that although there is visible dysfunction seen on echocardiography, persistent occlusion would result in a smaller area of irreversibly damaged myocardium or a significant delay in irreversible cell injury because of the preceding ischemia.

Another potential explanation is the presence of collateral circulation (23). Collateral circulation is thought to develop in the presence of a pressure gradient between the coronary bed distal to an obstruction and a normal or minimally diseased contralateral coronary artery (24). Coronary angiography does not estimate the presence or extent of collateral circulation well, limiting interpretation of studies utilizing angiographic data to assess differences in outcome related to collateral flow (25). Clinically significant collateralization that limits ventricular dysfunction was excluded in our study because any patient whose LVWMI did not change with the initial occlusion was excluded from the analysis. Techniques such as myocardial contrast echocardiography may help determine the role of collateral circulation in limiting infarct size in patients with preinfarction angina.

**Study limitations.** It is possible that longer ischemic periods, longer recovery periods or repetitive episodes of transient ischemia before minimally invasive CABG may be required to produce mechanical preconditioning in humans. In addition,
rather than preservation of systolic function, preconditioning may limit the metabolic and pathologic effects of prolonged ischemia, which were not measured in the current study.

Our sample size was small. Using the Wilcoxon signed rank test, our sample size had a 66% power to detect a change in LVWMS between occlusions 1 and 2. Although our data suggest that 24 patients would be required to exclude a difference between the two stages with 80% certainty, we observed a trend toward worse LVWMS during occlusion 2. Thus, our data are consistent with the concept that the initial 5-min ischemic period did not limit subsequent ischemic regional dysfunction.

Implications. Ischemic preconditioning could be of value in minimally invasive CABG. One potential benefit of preconditioning would be less systolic dysfunction and greater hemodynamic stability during occlusion of the native coronary artery for conduit anastomosis. Another potential benefit would be smaller infarct size should coronary occlusion or thrombosis of the vessel occur during the surgical procedure. The current study shows that a 5-min occlusion of the LAD did not result in less systolic dysfunction during the coronary anastomosis. In fact, coronary occlusion resulted in severe hypokinesia, akinesia and dyskinesia during both occlusions. Thus, surgeons should not expect a brief period of occlusion to protect against severe regional systolic dysfunction during coronary occlusion. Although the 5-min preliminary occlusion of the LAD did not prevent regional dysfunction during the subsequent occlusion, hemodynamic variables and regional dysfunction (LVWMS and LVWMI) tended to stabilize during the second occlusion, which was longer in duration. Potentially, LVWMI and LVWMS would have been greater during the second occlusion if test occlusions were not performed. Finally, in all patients from our series, complete systolic recovery was observed by TEE in the early postanastomosis period. Test occlusions may help permit the early mechanical recovery of systolic function after revascularization despite our finding of comparable dysfuction during both occlusion periods.

The metabolic effects of coronary occlusion were not assessed during the present study. In a recent study (13), intracoronary adenosine pretreatment limited the ischemic effects of PTCA as assessed by intracoronary and surface ECGs. Future studies assessing the effects of adenosine pretreatment on left ventricular function after coronary occlusion during minimally invasive CABG and PTCA are needed to define the clinical significance of this finding. In addition, it is unclear whether medical interventions that alter hemodynamic variables may improve systolic function or promote preconditioning during minimally invasive CABG.

We gratefully acknowledge the expert statistical analysis of Diane A. Vido, MS, Research Data Analyst.

References