Value of Delayed-Enhancement Cardiovascular Magnetic Resonance Imaging in Predicting Myocardial Viability After Surgical Revascularization

Joseph B. Selvanayagam, MBBS, FRACP; Attila Kardos, MD, PhD; Jane M. Francis, DCRR, DNM; Frank Wiesmann, MD; Steffen E. Petersen, MD; David P. Taggart, MD, PhD; Stefan Neubauer, MD, FRCP

Background—Despite the accepted utility of delayed-enhancement MRI in identifying irreversible myocardial injury, no study has yet assessed its role as a viability tool exclusively in the setting of coronary artery bypass surgery (CABG), and no study has repeated delayed-enhancement MRI late after revascularization. In a clinical trial in which patients underwent CABG by either the off-pump or on-pump surgical technique, we hypothesized that (1) preoperative delayed-enhancement MRI would have high diagnostic accuracy in predicting viability and (2) the occurrence of perioperative myocardial necrosis would affect late regional wall motion recovery.

Methods and Results—Fifty-two patients undergoing multivessel CABG were studied by preoperative and early (day 6) and late (6 months) postoperative cine MRI for global and regional functional assessment and delayed-enhancement MRI for assessment of irreversible myocardial injury. Preoperatively, 611 segments (21%) had abnormal regional function, whereas 421 segments (14%) showed evidence of hyperenhancement. At 6 months after revascularization, 57% (343 of 611) of dysfunctional segments improved contraction by at least 1 grade. When all preoperative dysfunctional segments were analyzed, there was a strong correlation between the transmural extent of hyperenhancement and the recovery in regional function at 6 months ($P < 0.001$). Of a total of 96 previously dysfunctional but nonenhancing or minimally hyperenhancing myocardial segments that did not improve regional function at 6 months, 35 (36%) demonstrated new perioperative hyperenhancement in the early postoperative MRI scan.

Conclusions—Delayed-enhancement MRI is a powerful predictor of myocardial viability after surgery, suggesting an important role for this technique in clinical viability assessment. *(Circulation. 2004;110:1535-1541.)*

Key Words: imaging • coronary disease • surgery • myocardium

Detecting viable but dysfunctional myocardium, whether stunned or hibernating, is critical to the management of patients with coronary artery disease because successful revascularization in such cases improves left ventricular (LV) function and prognosis. Delayed-enhancement MRI (DE-MRI) has been shown in several studies to be effective in identifying the presence, location, and extent of acute and chronic irreversible myocardial injury. To date, however, only one study has systematically evaluated the role of DE-MRI in predicting myocardial viability in coronary artery disease patients after revascularization. Kim et al showed, in a population with ischemic LV dysfunction, that the transmural extent of delayed hyperenhancement (HE) predicts the recovery of regional function after percutaneous or surgical intervention. Although this landmark study has been important in highlighting DE-MRI as a viability assessment tool, a number of questions need to be addressed about the utility of this technique in widespread cardiology practice. First, confirmation of the remarkable correlation between degree of preoperative transmural HE and late regional recovery at more than one cardiovascular magnetic resonance (CMR) center is necessary. Second, no study has correlated postsurgical DE-MRI findings with late functional changes. Therefore, it is unknown to what extent surgery-related irreversible injury affects late regional myocardial function. Third, the only study available on the subject has used a relatively short follow-up interval (3 months), ie, a time at which the true rate of functional recovery, particularly in hibernating segments, may have been underestimated.

We recently reported that in low-risk patients randomized to undergo CABG using either the on-pump (ONCABG) or off-pump (OPCABG) techniques, OPCABG surgery results in significantly better LV function early (6 days) after surgery when assessed by cine MRI. However, despite confirming

Received February 18, 2004; de novo received April 22, 2004; accepted May 18, 2004.

From the University of Oxford Centre for Clinical Magnetic Resonance Research (J.B.S., S.E.P., J.M.F., A.K., F.W., S.N.), and the Departments of Cardiovascular Medicine (J.B.S., S.E.P., J.M.F., A.K., F.W., S.N.) and Cardiothoracic Surgery (D.P.T.), University of Oxford, John Radcliffe Hospital, Oxford, UK.

Presented in part by Dr Selvanayagam at the American College of Cardiology Meeting, New Orleans, La, March 7–10, 2004.

Correspondence to Stefan Neubauer, MD, FRCP, Professor of Cardiovascular Medicine, Department of Cardiovascular Medicine, Level 5, John Radcliffe Hospital, Oxford, OX3 9DU, UK. E-mail stefan.neubauer@cardiov.ox.ac.uk

© 2004 American Heart Association, Inc.

*Circulation* is available at http://www.circulationaha.org  DOI: 10.1161/01.CIR.0000142045.22628.74
earlier studies that postoperative troponin release was significantly lower in the OPCABG group, we found no significant difference in the incidence and magnitude of surgery-related irreversible myocardial injury when assessed by DE-MRI.

Taking advantage of this unique cohort of CABG patients studied serially (before surgery and 1 week and now 6 months after surgery), the purpose of the present study was twofold: Our primary goal was to evaluate the usefulness of DE-MRI in an exclusively surgical population and to investigate the impact of surgery-related irreversible injury on late regional myocardial function and viability. We hypothesized that DE-MRI would have high diagnostic accuracy in predicting viability and that the rate of perioperative necrosis would affect regional wall motion (RWM) recovery. A secondary goal of this study was to assess the long-term effects of ONCABG and OPCABG surgery on regional and global LV function at 6 months after the operation. Given our earlier finding of no significant differences between the 2 groups in terms of MRI-defined perioperative irreversible myocardial injury, our hypothesis was that there would be no differences between the surgical groups in the late postoperative global LV function.

Methods

Ethics
The study was approved by our institutional ethics committee, and informed written consent was obtained from each patient. The study was performed according to the principles of the Declaration of Helsinki.

Patients
As described in our previous publication, of a total of 111 screened patients referred for isolated coronary grafting, 30 patients were randomized to undergo surgery with the OPCABG technique, and 30 were randomly assigned to undergo surgery with the ONCABG technique (Figure 1). We excluded patients with the following characteristics: age >75 years, severe preexisting LV dysfunction, involvement in other clinical trials, typical MRI contraindications (eg, pacemaker, severe claustrophobia, etc), and baseline creatinine >200 μmol/L.

CMR Follow-Up
Five patients did not undergo both the early and late postoperative scans, either because of serious postoperative morbidity (2 patients) or because they withdrew consent for further participation in the study. Two further patients declined the second follow-up CMR scan, and another patient could not undergo this scan because of implantable defibrillator insertion 2 months after surgery (Figure 1). Hence, a total of 55 patients (92%) underwent a second CMR scan at a median follow-up of 6 days (interquartile range, 4 to 17 days), and a total of 52 patients (87%) underwent a third CMR scan at a median follow-up of 179 (interquartile range, 170 to 188) days.

Clinical Follow-Up
At 6 months, the distribution of patients in the Canadian Cardiovascular Society (angina) classes and New York Heart Association (heart failure) classes were similar in the 2 groups. There were no deaths. There were no clinically reported myocardial infarctions or cerebrovascular accidents in either surgical group between hospital discharge and 6 months.

Treatment and Procedures
This has been described in detail previously. Briefly, all surgery was performed by the same surgeon (D.P.T.), experienced in both OPCABG and ONCABG surgery. The aim of surgery was to obtain complete arterial revascularization using both internal mammary arteries and the radial artery. Both surgical groups received a standardized anesthetic technique.

CMR Protocol
Patients were studied in a 1.5-T clinical MR scanner (Siemens Sonata), and steady-state free-precession cine images (TE/TR, 1.5/
Postprocessing Analysis

For global LV functional analysis, all short-axis slices from the base to the apex were analyzed with Argus software, version 2002B (Siemens) by an experienced observer blinded to surgical randomization and HE findings. The following parameters were determined by planimetry of all the short-axis images: LV end-diastolic volume index (in mL/m²), LV end-systolic volume index (in mL/m²), LV ejection fraction (in percent), and LV mass (in grams). Cardiac index (in L · min⁻¹ · m⁻²) was then calculated using the heart rate and stroke volume index. RWM was analyzed by a separate, experienced observer blinded to the DE-MRI finding and surgical randomization. RWM was graded as 0, normal; 1, mild or moderate hypokinesia; 2, severe hypokinesia; 3, akinesia; and 4, dyskinesia. Areas of late gadolinium-DTPA HE were graded in transmural extent (0, no HE; 1, 1% to 25% HE; 2, 26% to 50% HE; 3, 51% to 75% HE; and 4, >76% HE) and quantified by use of computer-assisted planimetry on each of the short-axis images. Hyperenhanced pixels were defined as those with image intensities >2 SD above the mean of image intensities in a remote myocardial region in the same image.¹¹

Definition of Segments

For cine and DE-MRI analysis, we used a 56-segment LV model (8 segments per short axis (SA) image; 7 SA images per patient). Segment 1 was defined at the anterior insertion of the right ventricle into the interventricular septum, and the next 7 segments proceeded in a clockwise manner. Segments 2 and 3 (at each SA image) were considered to represent the territory of the left circumflex artery, segments 4 to 6 the territory of the right coronary artery, and segments 7 to 1 the territory of the left anterior descending coronary artery.

Statistical Analysis

Continuous variables are expressed as mean (±SD) or median (interquartile range, 25% to 75%) as appropriate. A χ² test for trend and a logistic regression model with a repeated-measures variable for the patient (to adjust for the nonindependence of the data) were used to assess the relationship between the transmural extent of HE and improvement in regional function. The change in the LV volumes after ONCABG surgery was compared with the change after OPCABG surgery by use of the paired t test. Continuous variables that were not distributed normally were compared by use of the Mann-Whitney U test, and a correlation between such variables was made by use of the Spearman rank test. To assess for interobserver and intraobserver differences in the assessment of RWM grade, Cohen’s κ values were used. A probability value of P<0.05 was considered statistically significant.

Results

Global LV Function Before and After Surgical Revascularization

For the entire study group (n=52), the cardiac index (in L · min⁻¹ · m⁻²) rose significantly, from 2.9±0.8 preoperatively to 3.3±0.6 at 6-month follow-up (P=0.04). As shown in the Table, the mean preoperative ejection fraction was 62±12%, and the mean ejection fraction at 6 months was 67±10%.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>ONCABG</th>
<th>OPCABG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI preop,†</td>
<td>2.9±0.8</td>
<td>2.9±0.7</td>
<td>2.9±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>CI early postop,†</td>
<td>2.9±0.7</td>
<td>2.7±0.6</td>
<td>3.2±0.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Cl late postop, L · min⁻¹ · m⁻²</td>
<td>3.3±0.6*</td>
<td>3.3±0.6*</td>
<td>3.3±0.5*</td>
<td>NS</td>
</tr>
<tr>
<td>EDVI preop,† mL/m²</td>
<td>79±19</td>
<td>79±21</td>
<td>78±17</td>
<td></td>
</tr>
<tr>
<td>EDVI early postop,† mL/m²</td>
<td>78±19</td>
<td>79±22</td>
<td>77±17</td>
<td></td>
</tr>
<tr>
<td>ESVI late postop, mL/m²</td>
<td>76±19</td>
<td>76±19</td>
<td>75±18</td>
<td></td>
</tr>
<tr>
<td>EDVII preop,† mL/m²</td>
<td>30±15</td>
<td>30±15</td>
<td>30±15</td>
<td></td>
</tr>
<tr>
<td>ESVI early postop,† mL/m²</td>
<td>29±15</td>
<td>33±15</td>
<td>26±14</td>
<td></td>
</tr>
<tr>
<td>ESVI late postop, mL/m²</td>
<td>26±13†</td>
<td>26±13†</td>
<td>25±14†</td>
<td></td>
</tr>
<tr>
<td>EF preop,† %</td>
<td>62±11</td>
<td>62±12</td>
<td>62±11</td>
<td></td>
</tr>
<tr>
<td>EF early postop, ‰</td>
<td>61±11</td>
<td>59±11</td>
<td>65±12</td>
<td></td>
</tr>
<tr>
<td>EF late postop, %</td>
<td>67±10</td>
<td>67±9</td>
<td>67±10</td>
<td></td>
</tr>
<tr>
<td>LV mass preop, ‰</td>
<td>135±34</td>
<td>140±36</td>
<td>132±33</td>
<td></td>
</tr>
<tr>
<td>LV mass early postop, ‰</td>
<td>135±30</td>
<td>140±36</td>
<td>133±32</td>
<td></td>
</tr>
<tr>
<td>LV mass late postop, ‰</td>
<td>132±30</td>
<td>135±36</td>
<td>129±32</td>
<td></td>
</tr>
</tbody>
</table>

Irreversible Injury Assessed by DE-MRI

As previously described, 30 patients (50%) had some evidence of HE in their preoperative scan, with a mean mass of 19.1±12.0 g.⁹ Early postoperatively, 21 patients had evidence of new HE, quantified at 6.5±4.1 g. At 6 months postoperatively, there were no new areas of HE noted in any patient compared with the early postoperative scan. However, there was a significant reduction in the magnitude of perioperative HE mass between the 2 postoperative scans (from 6.5±4.1 to 4.9±3.8; P<0.001), in keeping with remodeling changes after myocardial necrosis (Figure 2B). In contrast, in patients in whom there was evidence of scar (ie, chronic myocardial infarction) preoperatively but no new HE postoperatively, the total mass HE remained constant throughout the 2 postoperative scans, indicating that the magnitude of scar remained unchanged. Figure 3 shows an example of a patient with scar before surgery, which remains unchanged after surgery.

Prediction of Myocardial Viability

To evaluate whether DE-MRI predicted recovery of regional function after CABG, we matched the DE-MRI and RWM findings in a total of 2471 myocardial segments corresponding to the vessels that were revascularized. Preoperatively, 611 segments (21%) had abnormal regional function, whereas 421 segments (14%) had some evidence of HE. Six months after revascularization, 59% (359 of 611) of dysfunctional segments improved contraction by at least 1 grade. The
transmural extent of HE correlated closely with the likelihood of improvement in regional function after surgery (Figure 4). When all segments that were dysfunctional preoperatively were analyzed, the proportion with improved regional function decreased as the transmural grade of HE increased (P<0.001). For example, regional function improved in 156 of 190 segments (82%) with no preexisting HE but in only 16 of 63 segments (25%) with 51% to 75% HE and 1 of 25 segments (4%) with >76% HE. This relationship between the transmural extent of HE and the improvement in regional function was present irrespective of the degree of preoperative segmental dysfunction (Figure 4).

**Relationship of New Perioperative HE to Regional Function at 6 Months**

To investigate the impact of surgery-related irreversible injury on late regional myocardial function and viability, we systematically analyzed segments with no or minimal HE (pre-CABG) in which the RWM worsened at 6 months. In the 362 preoperatively dysfunctional segments with no HE or only 1% to 25% HE, a total of 96 myocardial segments (27%) did not improve regional function at 6 months (Figure 4). Of these 96 segments, 35 (36%) demonstrated new perioperative HE in the early postoperative MRI scan, indicating that the occurrence of perioperative myocardial necrosis accounts for a portion of segments failing to improve late regional function. Conversely, 61 segments (64%) failed to recover further despite not showing any surgery-related HE. Furthermore, of 2050 revascularized segments with normal contraction and no HE preoperatively, another 121 segments (6%) demonstrated new HE (in early postoperative MRI) and new RWM abnormalities at 6 months. Of these segments, 86 (71%) demonstrated mild/moderate hypokinesis, 30 (25%) demonstrated severe hypokinesis, and 5 (4%) demonstrated akinesis.

**Interobserver/Intraobserver Variability for RWM Scoring and HE Grade**

The first 30 scans (1680 segments) were analyzed again by the first observer after a 6-month period. The κ value for this was 0.7 (SE, 0.02; P<0.0001), indicating that the degree of intraobserver agreement was good. The same segments were also analyzed by a second blinded investigator with moderate to good agreement (κ, 0.6; SE, 0.03; P<0.0001). For transmural grading of the 5 categories of HE in the same 30 scans, the κ value for assessment by a second investigator was 0.8 (SE, 0.01; P<0.0001), and there was a positive correlation (Spearman r=0.8; P<0.001) between the scores determined by the first and second observers.

**Effects of OPCABG Versus ONCABG Surgery on Global LV Function at 6 Months**

As previously reported,9 the mean preoperative cardiac index was similar in the 2 surgical groups (2.9±0.7, ONCABG; 2.9±0.8, OPCABG; P=0.9), whereas the early postoperative CI was significantly higher in the OPCABG group (2.7±0.6, ONCABG; 3.2±0.8, OPCABG; P=0.04).9 As shown in the Table, the cardiac index at 6 months was 3.3±0.5 mL·min⁻¹·m⁻² in the OPCABG group and 3.3±0.6 mL·min⁻¹·m⁻² in the ONCABG group (P>0.05). There was significant improvement in the cardiac index in both surgical groups at 6 months postoperatively compared with preoperative values (P=0.04). This improvement in cardiac function occurred as a result of a significant reduction in the end-systolic volume index at 6 months in both surgical groups (P=0.02 for both groups). There was no change in the end-diastolic volume index at 6 months, although there was a downward trend (toward smaller volumes) in both surgical groups.

**Discussion**

**Prediction of Myocardial Viability by DE-MRI**

In a cohort of patients undergoing exclusive surgical revascularization, our results confirm the primary hypothesis that the transmural grade of HE was significantly related to the likelihood of improvement in regional function 6 months after surgery, irrespective of the preoperative regional function. In this respect, our results confirm the only previous study on this subject, by Kim et al.7 They found that when all dysfunctional segments were considered in a cohort of 41 patients undergoing revascularization by either percutaneous transluminal coronary angioplasty or CABG, the likelihood of improvement in regional function after revascularization decreased progressively as the transmural extent of HE before the time of surgery was increased.
revascularization increased. Kim et al reported regional function improvement at 3 months of 78% in segments without HE, 59% in segments with 1% to 25% HE, but improvement in only 2% in segments with >25% HE. We found that regional function improved in 82% of segments with no preexisting HE, 64% segments with 1% to 25% HE, and 37% of segments with 26% to 50% HE. The percentage of segments (with no, or <25% HE) with improved regional function in our study is slightly higher than that observed by Kim et al and is more likely to be closer to the true rate of functional recovery, because our follow-up scan was at 6 months rather than at 3 months after revascularization, as in that study.

We ascertained the predictive accuracy of preoperative transmural HE for the recovery of late regional function in a cohort “typical” (ie, with a mean age of 60 years with at least moderately preserved LV function and without major comorbidity) of most patients referred for bypass surgery. If we used a cutoff value of <25% HE, we obtained a positive predictive value of 73% and a negative predictive value of 69% when all dysfunctional segments were considered. Studies that have evaluated the prediction of viability using thallium scintigraphy and dobutamine echocardiography have consistently shown higher negative predictive values for the former and higher positive predictive values for the latter. Although no study has yet compared these 2 imaging techniques directly with DE-MRI, our findings place DE-MRI (when using <25% HE as a cutoff for viability) as having higher positive predictive value than thallium scintigraphy (but lower than dobutamine echocardiography) and higher negative predictive value than dobutamine echocardiography (but lower than thallium scintigraphy). When only segments with severe preoperative dysfunction (ie, severe hypokinesia, dyskinesia, or akinesia) were considered in our study, the positive and negative predictive values were higher, at 81% and 72%, respectively. The ability of DE-MRI to evaluate those segments that have severe dysfunction before surgery (and often the most difficult to evaluate with other imaging techniques) with high diagnostic accuracy is one of the strengths of this technique. The addition of low-dose dobutamine stress MRI to the DE-MRI protocol may further increase the diagnostic accuracy for viability detection, and future studies are awaited.

Similar to the findings reported by Kim et al, we also observed that there were a significant number of patients in our study who failed to demonstrate an improvement in late regional function, despite having no or minimal HE in their segments.
preoperative scan. Possible explanations for this are incomplete revascularization because of diffuse atherosclerotic disease; tethering of viable myocardial regions to adjacent scarred segments, resulting in viable regions having an incomplete response; and limitations in the imaging technique. In addition, our DE-MRI results obtained after surgery indicate that the occurrence of perioperative myocardial necrosis may also be responsible for some of the lack of functional recovery seen in patients who have no or minimal HE in their preoperative scan. We find that of all the dysfunctional myocardial segments with no or minimal HE before surgery that failed to improve regional function at 6 months, approximately one third of segments demonstrated new HE after surgery. New RWM abnormality was also noted in 6% of previously normally contracting, nonhyper-enhancing segments as a result of perioperative HE.

We failed to demonstrate any new regions of HE in any patient between 1 week and 6 months postoperatively. Almost all patients in our study received arterial grafts exclusively, with a mean number of 2.6 grafts per patient. Graft failure would be the most likely (although not the only) reason for the presence of new irreversible injury after the first week after surgery. Our finding of no new irreversible injury after the early postoperative scan strongly suggests that graft failure is rare after total arterial revascularization and is in keeping with high angiographic early patency rates obtained by Endo et al and by Calafiore et al. Furthermore, in patients in whom there was evidence of scar preoperatively but no new HE postoperatively, there was no change in the total magnitude of HE across the 2 postoperative scans, confirming the excellent reproducibility of the DE-MRI technique reported by other groups.

**ONCABG Versus OPCABG Surgery**

The second aspect of our study was to compare late changes in LV function in patients randomized to ONCABG and OPCABG coronary surgery. Our results confirm the secondary hypothesis that there are no differences in late postoperative LV function between the 2 surgical groups. Both surgical groups had a significant improvement in global cardiac function at 6 months. Compared with the preoperative cardiac index, there was an absolute improvement of 0.4 L·min⁻¹·m⁻² (or 12% of preoperative CI) in the 6-month mean cardiac index in both surgical groups. Therefore, OPCABG surgery improves LV function early after surgery, but at 6 months, both surgical groups show a similar benefit in LV function from revascularization. These results may also provide an explanation for a previous randomized study that failed to demonstrate any differences in cardiac clinical outcome at 1 year in a low-risk population randomized to the 2 surgical techniques.

We also found that both surgical techniques resulted in a significant improvement in global LV function at 6 months compared with the preoperative LV function. This illustrates that both surgical techniques are equally successful in recovering hibernating myocardial segments. Furthermore, this significant improvement in global LV function is seen in the setting of at least moderately preserved preoperative ejection fraction. Previous studies such as those by Righetti et al. using 2D echocardiography to assess changes in cardiac function, have failed to demonstrate a significant change in LV function in a group with previously normal LV function. The most likely explanation for the differences noted in our study is the much higher sensitivity of CMR for detecting changes in cardiac function compared with 2D echocardiography.

**Limitations**

Our study has several limitations. First, we used a 56-segment model rather than the recently proposed 17-segment model to grade affected segments. Our rationale for this was that because the likely areas of new HE were expected to be small, we wanted to use a model that encompassed smaller segments, so that we could more closely match the occurrence on new myocardial HE after surgery with RWM changes. However, by increasing the number of segments, we are more prone to misregistration errors in the serial analysis of data. Furthermore, misregistration might also have occurred as a result of through-plane motion of the LV, particularly because the global ventricular function was good in a majority of patients. Moreover, as with all functional indices based on myocardial deformation, direct visual assessment of RWM is load dependent, and in particular, afterload dependent. Thus, in the regionally infarcted LV, the mechanical behavior of infarcted subendocardial myocardium is in large part dictated by that of the preserved subepicardial layers. Load independence at both the global and regional levels is an important limitation in interpreting viability studies of this nature. In conclusion, we have demonstrated that DE-MRI is a powerful predictor of myocardial viability after surgery, suggesting an important role for this technique in clinical viability assessment. We have further shown that although OPCABG surgery results in better LV function in the early postoperative period compared with ONCABG surgery, at 6 months after surgery, both groups show a similar and significant benefit from revascularization.

**Acknowledgments**

This work was supported by the British Heart Foundation and the Medical Research Council, UK. Dr Selvanayagam is funded by the Wellcome Trust.

**References**


Value of Delayed-Enhancement Cardiovascular Magnetic Resonance Imaging in Predicting Myocardial Viability After Surgical Revascularization
Joseph B. Selvanayagam, Attila Kardos, Jane M. Francis, Frank Wiesmann, Steffen E. Petersen, David P. Taggart and Stefan Neubauer

_Circulation_. 2004;110:1535-1541; originally published online September 7, 2004; doi: 10.1161/01.CIR.0000142045.22628.74
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/12/1535

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/