Effects of Off-Pump Versus On-Pump Coronary Surgery on Reversible and Irreversible Myocardial Injury

A Randomized Trial Using Cardiovascular Magnetic Resonance Imaging and Biochemical Markers

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Background—There is biochemical evidence that off-pump coronary artery bypass grafting (OPCABG) reduces myocardial injury compared with the use of cardiopulmonary bypass (ONCABG), but the functional significance of this is uncertain. We hypothesized that OPCABG surgery would result in reduced postoperative reversible (stunning) and irreversible myocardial injury, as assessed by cardiovascular MRI (CMRI).

Methods and Results—In a single-center randomized trial, 60 patients undergoing multivessel total arterial revascularization were randomly assigned: 30 to OPCABG and 30 to ONCABG. Patients underwent preoperative and early postoperative cine MRI for assessment of global left ventricular function, and contrast-enhanced CMRI for assessment of irreversible myocardial injury. Serial troponin I measurements were obtained perioperatively and correlated with the CMRI findings. The mean preoperative cardiac index was similar in the 2 surgical groups (2.9±0.7 ONCABG; 2.9±0.8 OPCABG; \(P=0.9\)). After surgery, the cardiac index was significantly higher in the OPCABG group (2.7±0.6 ONCABG; 3.2±0.8 OPCABG; \(P=0.04\)). New irreversible myocardial injury was similar in incidence (36% ONCABG; 44% OPCABG; \(P=0.8\)) and magnitude (6.3±3.6 g ONCABG; 6.8±4.0 g OPCABG; \(P=0.9\)) across the 2 groups. The median area-under-the-curve (AUC) troponin I values were significantly larger in the ONCABG group (182 versus 135 \(\mu\)g/L; \(P=0.02\)). There was a moderate correlation between the troponin I AUC values and mean mass of new myocardial hyperenhancement \((r^2=0.4; P=0.008)\).

Conclusions—OPCABG results in significantly better left ventricular function early after surgery but does not reduce the incidence or extent of irreversible myocardial injury. (Circulation. 2004;109:345-350.)

Key Words: surgery ■ imaging ■ magnetic resonance imaging ■ myocardial stunning

Coronary artery bypass grafting (CABG) is highly effective in improving life expectancy and quality of life for patients with ischemic heart disease and consequently is one of the most commonly performed major operations in the industrialized world. Until recently, CABG was performed almost exclusively with cardiopulmonary bypass (CPB) and cardiac arrest, thereby providing a motionless and bloodless surgical field to allow construction of the anastomoses in optimal conditions. Yet conventional “on-pump” CABG (ONCABG) carries 2 relatively low but well-recognized risks. The use of CPB leads to a systemic inflammatory response syndrome and multiorgan dysfunction, whereas obligatory periods of ischemia during aortic cross-clamping result in myocardial damage despite advances in protective cardioprotective techniques.

The availability of improved stabilizing devices has led to a renewed interest in off-pump CABG (OPCABG), and currently it is estimated that 25% of all CABG in the United States is performed this way. OPCABG surgery eliminates the need for CPB and allows continuous perfusion of the beating heart with temporary periods of local ischemia while the target vessel is occluded. Although technically more demanding, there is evidence from both observational studies and randomized trials that OPCABG surgery leads to a significant reduction in release of cardiac enzymes compared with the conventional operation. Importantly, however, it is unknown whether this reduction in release of myocardial enzymes is associated with reduced perioperative myocardial stunning (reversible) or necrosis (irreversible), because en-
zyme release may be, at least in part, a result of increased turnover of cytoplasmic pools.

High-resolution cardiovascular magnetic resonance imaging (CMRI) is a novel, noninvasive, and safe technique that allows serial assessment of myocardial function and viability. Given its 3D nature and order-of-magnitude greater signal-to-noise ratio, cine MRI is highly superior to 2D echocardiography and has become the “gold standard” investigation for measurement of left ventricular (LV) volumes, mass, and function of both normal and abnormal ventricles. Contrast-enhanced CMRI allows assessment of the transmural extent of irreversible injury, as well as quantification of even small areas of myocardial necrosis, both as a result of native coronary disease and after percutaneous coronary intervention. Furthermore, recent reports have confirmed the power of contrast-enhanced CMRI in predicting recovery of regional wall function after revascularization.

Using this highly sensitive and reproducible technique, we compared the extent of perioperative myocardial reversible injury (stunning) and irreversible injury (necrosis) in patients undergoing multivessel CABG with and without CPB in a single-center randomized trial. To the best of our knowledge, this is the first such study using cine and contrast-enhanced CMRI. Furthermore, we correlated these CMRI findings with the changes in postoperative cardiac troponin I. Our primary hypothesis was that OPCABG surgery results in reduced myocardial stunning (as measured by cine MRI) in the early postoperative period compared with ONCABG surgery. We further hypothesized that OPCABG surgery is superior to ONCABG with regard to the extent of permanent myocardial damage and that postoperative myocardial enzyme release reflects myonecrosis.

Methods

Ethics
Our institutional ethics committee approved the study, and each patient gave informed, written consent.

Patients
Between May 2002 and February 2003, of a total of 111 screened patients referred for isolated coronary grafting, 30 patients were randomly assigned to undergo surgery with the on-pump technique, and 30 were randomly assigned to undergo surgery with the off-pump technique (see Figure 1). We excluded patients with the following criteria: age >75 years, severe LV dysfunction (ejection fraction <20% by echocardiogram), involvement in other clinical trials, typical MRI contraindications, and baseline creatinine >200 µmol/L. Patients were randomized only after successfully completing the first CMRI scan.

Treatment and Procedures
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. An intraoperative imaging system was used routinely to confirm graft patency.

Anesthesia
All patients received a standardized anesthetic technique comprising scopolamine, fentanyl, pancuronium, etomidate, and propofol. All patients received full heparinization (3 mg/kg).

Figure 1. Flow chart of screened patients who were then randomized for participation in study. LVF indicates severe LV failure; RF, renal failure; PPM, permanent pacemaker.

ONCABG
CPB was performed with nonpulsatile flow and a temperature of 34°C. A membrane oxygenator and alpha-stat control of acid-base management were used, and the mean arterial pressure was maintained at 50 to 60 mm Hg with pharmacological manipulation as necessary. Myocardial protection was obtained with 1 L of St Thomas’s cold (4°C) crystalloid cardioplegia delivered antegradely and repeated after 30 minutes as necessary.

OPCABG
Commercially available stabilizers were used. The coronary artery was snared proximally (but not distally) with a Silastic sling. Intravascular shunts were not used.

ECG
All patients underwent ECG assessment before surgery and 5 days after surgery.

Biochemistry
Cardiac troponin I was measured before surgery and at 1, 6, 12, 24, 48, and 120 hours after surgery. Samples were analyzed at the Department of Clinical Biochemistry, John Radcliffe Hospital, with an immunoassay analyzer (Immulet; Diagnostic Products Corp). The lower limit of quantification was 0.2 µg/L.

CMRI Protocol
Patients were studied in a 1.5-T clinical MRI scanner (Siemens Sonata), and steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°) were acquired in 2 long-axis and 8 to 10 short-axis views. The acquisition of short-axis views began 1 cm below the level of the mitral valve insertion plane and continued in 1-cm increments through the left ventricle. A commercially available gadolinium-based contrast agent (Gadodiamide, Omniscan, Nycomed Amersham) was then administered intravenously at a dose of 0.1 mmol/kg body wt, and contrast-enhanced images were acquired after a 10-minute delay with the use of an inversion-recovery segmented gradient echo sequence. Contrast-enhanced images were acquired in identical long- and short-axis planes to the cine images, except for the most apical short-axis slice, which was excluded because it can be affected by partial-volume effects. The inversion time was meticulously adjusted to obtain maximal nulling of remote normal LV myocardium with voxel sizes of 1.9×1.4×7.0 mm.

Postprocessing Analysis
Short-axis cine slices from the base to the apex were analyzed with Argus software, version 2002B (Siemens) by an experienced observer blinded to surgical randomization and hyperenhancement.
findings. The following parameters were determined by planimetry of all the short-axis images in end diastole and end systole: LV end-diastolic volume index (EDVI), LV end-systolic volume index (ESVI), LV ejection fraction, and LV mass. Cardiac index (in L·min⁻¹·m⁻²) was then calculated using the heart rate and stroke volume index. Areas of gadolinium contrast enhancement were quantified by 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.¹⁰

### Statistical Analysis

All data were analyzed on an intention-to-treat principle beginning immediately after randomization. Values are expressed as mean (±SD) or median (interquartile range, 25% to 75%) as appropriate. The change in the LV volumes after ONCABG surgery was compared with the change after OPCABG surgery by the unpaired t test. Dichotomous data were compared by the χ² statistic. Continuous variables that were not distributed normally were compared by the Mann-Whitney test, and correlation between such variables was made by the Spearman rank test. A probability value of P<0.05 was considered statistically significant.

### Results

#### Characteristics of Patients and Assignment of Treatment Groups

The preoperative characteristics of the 2 groups were similar with regards to age, sex, cardiovascular risk factors, and use of medication (Table 1). One patient randomly assigned to the OPCABG group was converted to ONCABG because intraoperative LV function was considered to be severely impaired. Therefore, 59 patients (98%) were treated according to the randomization protocol. No patients died. The mean number of distal anastomoses per patient was 2.8±0.9 in the OPCABG group and 2.9±0.8 in the ONCABG group. All grafts (77/77) in the OPCABG group and 97% (77/79) of grafts in the ONCABG group were arterial. Five of 60 (3 OPCABG; 2 ONCABG) patients needed postoperative inotropic support as defined by adrenaline use >5 μg·kg⁻¹·min⁻¹ for >8 hours. There was no statistically significant difference between the groups in the number of distal anastomoses used, use of arterial grafts, and postoperative inotropes. In the ONCABG group, the mean bypass time was 57±18 minutes, and the mean cross-clamp time was 41±13 minutes.

The median interval between the first CMRI scan and surgery was 1 (1–3) day in the ONCABG group and 1 (1–2) day for the OPCABG group (P=0.8), and the median interval between the surgery and the second CMRI scan was 6 (4–16) days and 6 (5–10) days (P=0.8), respectively.

#### ECG Results

Overall, 21 patients (35%) of the study population had pathological Q waves on preoperative ECG. Of these, 12 (40%) were in the ONCABG group and 9 (30%) in the OPCABG group (P=0.5). Two patients (7%) in the OPCABG group and 2 (7%) in the ONCABG group developed new ECG Q waves after surgery. All 4 of these patients had evidence of new hyperenhancement by contrast-enhanced CMRI. Conversely, 17 patients with new hyperenhancement did not develop new Q waves on ECG.

#### CMRI Results

Two patients (1 from each group) could not undergo a follow-up scan as a result of serious postoperative morbidity (1 ONCABG patient with a cerebrovascular event and 1 OPCABG patient with prolonged respiratory failure). Three other patients (2 ONCABG; 1 OPCABG) declined the follow-up CMRI scan. Hence, a total of 55 patients (92%) underwent a second CMRI scan at a median follow-up of 6 (4–17) days. Of these 55 patients, 2 (1 from each group) underwent only cine MRI in their second scan, because they declined repeat gadolinium administration.

#### Cine MRI

As shown in Table 2, the mean preoperative cardiac index was similar in the 2 surgical groups. However, after surgery, the cardiac index was significantly higher in the OPCABG group (P=0.04). The mean preoperative ejection fraction was 62±12% in the ONCABG group and 62±11% in the OPCABG group (P=0.9). After surgery, this decreased to 59±11% in the ONCABG group and increased to 65±12% in the OPCABG group, resulting in a significant absolute ejection fraction difference of 6% between the 2 surgical groups (P=0.03). Before surgery, LV EDVI and LV ESVI were similar for both groups. Although postoperative LVEDVI was not significantly different between the 2 groups, postoperative LV ESVI decreased significantly, by 13%, in the OPCABG group (P=0.02), indicating that lower end-systolic volumes were the main reason for the improved LV function in this group.

There were no significant differences in total LV mass or patient weight either between groups or before and after surgery (Table 2).

#### Contrast-Enhanced CMRI

The preoperative CMRI scan showed myocardial hyperenhancement in 16 patients (53%) in the ONCABG group and
TABLE 2. Preoperative and Postoperative LV Function, Mass, and Patient Weight

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=60)</th>
<th>ONCABG (n=30)</th>
<th>OPCABG (n=30)</th>
<th>P</th>
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<tbody>
<tr>
<td>Cl, L·min⁻¹·m⁻²</td>
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<tr>
<td>Preop</td>
<td>2.9±0.8</td>
<td>2.9±0.7</td>
<td>2.9±0.8</td>
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<tr>
<td>Postop</td>
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<td>EDVI, mL/m²</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>79±19</td>
<td>79±21</td>
<td>78±17</td>
<td>NS</td>
</tr>
<tr>
<td>Postop</td>
<td>78±19</td>
<td>79±22</td>
<td>77±17</td>
<td>NS</td>
</tr>
<tr>
<td>Δ, %</td>
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<td>0</td>
<td>-3</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
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<td></td>
<td></td>
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<td>30±15</td>
<td>30±15</td>
<td>30±15</td>
<td>NS</td>
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<tr>
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<td>26±14</td>
<td>NS</td>
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<tr>
<td>Δ, %</td>
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<tr>
<td>EF, %</td>
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<tr>
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<td>62±12</td>
<td>62±11</td>
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</tr>
<tr>
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<td>59±11</td>
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</tr>
<tr>
<td>Δ, %</td>
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<td>-3</td>
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<td>0.03</td>
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<tr>
<td>LV mass, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>135±34</td>
<td>140±36</td>
<td>132±33</td>
<td>NS</td>
</tr>
<tr>
<td>Postop</td>
<td>135±30</td>
<td>140±36</td>
<td>133±32</td>
<td>NS</td>
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<tr>
<td>New HE myocardium, g</td>
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<td>6.3±3.6</td>
<td>6.8±4.0</td>
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<tr>
<td>Weight, g</td>
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<td></td>
<td></td>
</tr>
<tr>
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<tr>
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<td>81±10</td>
<td>83±10</td>
<td>79±9</td>
<td>NS</td>
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</table>

Plus-minus values represent mean±SD. NS denotes not significant (P>0.05); Cl, cardiac index; EF, ejection fraction; HE, hyperenhanced; Preop, preoperative; and Postop, postoperative.

14 (47%) in the OPCABG group. Assuming a myocardial specific gravity of 1.05 g/cm³, the mean mass of hyperenhanced tissue in these patients was 19.2±10.7 g (ONCABG) and 19.1±14.2 g (OPCABG). Nine of 26 patients (35%) in the ONCABG group had evidence of new hyperenhancement in their postoperative scan, with a mean hyperenhancement mass of 6.3±3.6 g. In the OPCABG group, 12 of 27 patients (44%) had evidence of new myocardial hyperenhancement, with a mean mass of hyperenhancement of 6.8±4.0 g (P=NS for comparison of both magnitude and incidence of new hyperenhancement between the 2 groups). When all patients were included in the analysis, ONCABG surgery resulted in a mean loss of myocardium of 2.3±3.8 g, whereas OPCABG surgery resulted in a mean loss of myocardium of 3.2±4.4 g (P=0.5). Patients with new Q waves after surgery had a mean (new) contrast-enhanced mass of 8.5±4.1 g, whereas patients without new ECG Q waves had a mean (new) contrast-enhanced mass of 6.1±3.1 g (P=0.5), indicating that the ECG Q waves are an insensitive marker of irreversible myocardial injury.

In patients with new hyperenhancement, there was a similar pattern of distribution in both groups. Eight of 9 patients (89%) with new hyperenhancement in the ONCABG group and 11 of 12 (92%) in the OPCABG group had new hyperenhancement in a previously normal area located in the apical one third of the myocardium (ie, in the 3 most apical short-axis slices imaged after contrast). Figure 2 shows examples of this pattern of hyperenhancement in a patient after OPCABG surgery.

In the ONCABG group, when patients without new hyperenhancement were considered, there was a significant correlation between the change in preoperative and postoperative ESVI (Δ ESVI) and the cross-clamp time (r²=0.6, P=0.02). In the same group, there was a nonsignificant trend between Δ ejection fraction and cross-clamp time (r²=0.5, P=0.1).

Troponin I Results
The median area-under-the-curve (AUC) values for troponin I release were significantly higher in the ONCABG group...
The most likely explanation is that aortic clamping induces global marked activation of systemic inflammatory responses, the large ischemia-reperfusion injury and a more severe degree of myocardial stunning with longer intraoperative ischemic time.

Contrary to our secondary hypothesis, OPCABG surgery failed to reduce either the incidence or extent of irreversible myocardial injury compared with ONCABG surgery. Indeed, new irreversible injury was remarkably similar in both surgical groups, in incidence ($\approx$40%), magnitude ($\approx$6.5 g), and distribution (90% of patients demonstrated new hyperenhancement in the apical myocardium). Myonecrosis in the setting of successful coronary artery bypass surgery may result from native or graft vessel closure, hypoperfusion, distal embolization of atheromatous material, or inadequate myocardial protection. In our study population, myonecrosis was unlikely to be the result of intraoperative graft failure, because patients routinely had confirmation of intraoperative graft patency with an imaging system based on fluorescence of indocyanine green. Given the relatively small amount of injury detected and its apical location, it is unlikely to be a result of postoperative graft failure. We speculate that the most likely mechanism for myonecrosis is inadequate distal myocardial preservation with on-pump cardioplegia and reduced distal myocardial wall perfusion with OPCABG surgery. Whether different cardioplegic techniques in the ONCABG group or the use of intracoronary shunts in the OPCABG group could reduce such injury merits further investigation.

Overall, CABG surgery in our population resulted in only a small (3 g, or 2%) loss of LV myocardium. This indicates that both techniques are excellent in minimizing irreversible myocardial injury. We are unaware of any similar published studies in a CABG population, but interestingly, our findings are similar to those of Ricciardi et al., who reported a median mass of new hyperenhancement of 3 g in those patients who demonstrated postprocedural elevation of creatine kinase (CK)-MB after percutaneous coronary intervention.

We found that OPCABG surgery results in significantly less cumulative release of serum troponin I than ONCABG surgery, when measured up to 5 days after the operation. This finding supports previously published studies. In the largest randomized trial to date, involving 281 patients, van Dijk et al. reported a significant reduction in the cumulative release of muscle brain fraction (CKMB) by 41% with OPCABG compared with ONCABG. The magnitude of troponin I release observed in our study correlated moderately well with the area of new hyperenhancement as detected by CMRI. Our biochemical findings confirm that large increases of serum troponin I in the setting of coronary surgery do indicate perioperative myonecrosis as indicated by contrast-enhanced CMRI. However, in patients with no new hyperenhancement, there was a wide spread of AUC troponin values, clearly indicating that not all of the postoperative serum troponin I release represents irreversible myocardial injury. It is tempting to speculate that some of the troponin leak probably represents protein release from non-structurally bound cytosolic pools, rather than true myocardial necrosis.
Limitations
There are several potential limitations to our study. First, in the absence of any previously reported CMRI studies in a CABG population, we chose a group representative of most patients referred for bypass surgery; ie, with a mean age of 60 years with at least moderately preserved LV function and without major comorbidity. Although the improved myocardial performance associated with OPCABG surgery may not translate into clinically significant benefits in this particular group of patients, similar findings in patients with markedly impaired LV function would be of major importance. This hypothesis, however, needs to be addressed in a separate trial of such a high-risk patient group. Second, postoperative scans were performed a median of 6 days after surgery and not earlier because of patient safety and tolerance concerns. Hence, the postoperative scan misses the period of maximum cardiac dysfunction during the first 24 to 48 hours after surgery and may therefore, in fact, underestimate the magnitude of difference between the groups. Third, myocardial protection may not have been optimal in either group. Randomized studies comparing the cardioprotective effects of blood versus crystalloid cardioplegia have produced conflicting results. It is possible that blood cardioplegia may have provided superior myocardial protection in the ONCABG group. We used cold crystalloid cardioplegia, however, because it is widely used and in the absence of definite clinical evidence of superiority of other regimens in uncomplicated CABG. Furthermore, in the OPCABG group, it is possible that intracoronary shunts may have improved distal myocardial protection. These were not used in our study, however, because they can be difficult to introduce and raise concerns about endothelial damage.

Conclusion
In conclusion, we have demonstrated that in low-risk patients undergoing isolated CABG, off-pump surgery results in better LV function early after surgery but does not reduce the incidence and extent of irreversible myocardial injury. The sensitivity of CMRI in the assessment of cardiac function and quantification of myonecrosis makes it a powerful tool in the investigation of pathophysiological mechanisms of myocardial injury and in the evaluation of potential cardioprotective strategies.

Acknowledgments
This work was supported by the British Heart Foundation and the Medical Research Council, UK. The Guidant and Medtronic companies provided funding for the analysis of the biochemical specimens. Dr Selvanayagam was funded by the Wellcome Trust. The authors are grateful for the support of David Pigott, Department of Anesthesia; Polly Whitworth, for help with the coordination of blood samples; and Dudley Pennell and James Moon, who provided training in gadolinium CMRI techniques for Dr Selvanayagam.

References
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_Circulation_. 2004;109:345-350; originally published online January 19, 2004;
doi: 10.1161/01.CIR.0000109489.71945.BD

_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

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