Linear Cryoablation of the Left Atrium Versus Pulmonary Vein Cryoisolation in Patients With Permanent Atrial Fibrillation and Valvular Heart Disease

Correlation of Electroanatomic Mapping and Long-Term Clinical Results

Fiorenzo Gaita, MD; Riccardo Riccardi, MD; Domenico Caponi, MD; Dipen Shah, MD; Lucia Garberoglio, MD; Laura Vivalda, MD; Alessandro Dulio, BS; Andrea Chiecchio, PhD; Eric Manasse, MD; Roberto Gallotti, MD

Background—The aim of this study was to clarify the role of pulmonary vein isolation (PVI) alone versus left atrial linear lesions in the treatment of permanent atrial fibrillation (AF) in patients with left atrial dilatation and valvular disease. The primary end point was to assess the persistence of sinus rhythm (SR) off antiarrhythmic drugs (AADs) at 2-year follow-up and to correlate clinical outcome with surgical results validated with electroanatomic mapping (EAM).

Methods and Results—A total of 105 patients with permanent AF undergoing valve surgery were assigned to 3 different groups: in groups “U” and “7,” left atrial linear cryoablation was performed, whereas in group “PV” patients, anatomic cryoisolation of pulmonary veins only was performed. In groups U and 7, SR was achieved in 57% of patients, whereas it was achieved in 20% of PV patients during 2-year follow-up. In the first 51 patients, the ablation schemes were validated with EAM. The EAM showed that the U lesion was never obtained: in 59% of these patients, a complete 7 lesion was achieved instead; in the 7 group, a complete 7 lesion was present in 65% of patients, whereas a complete PVI was obtained in 71% of patients. Considering patients in whom a complete 7 lesion was demonstrated with the EAM, SR without AADs was achieved in 86% of patients, whereas only 25% of patients with complete PVI were in SR without AADs.

Conclusions—In patients with permanent AF, left atrial dilatation and valvular heart disease linear lesions in the posterior region of the left atrium are more effective than PVI alone. With cryoablation, the surgical intent is fulfilled in only approximately 65% of the cases. Knowing the real anatomic and electrophysiological effects of surgical ablation is necessary to correctly interpret the clinical outcome. (Circulation. 2005;111:136-142.)

Key Words: cryoablation • fibrillation • heart disease

In the past decade, various ablative procedures, surgical or transcatheter, for treatment of atrial fibrillation (AF) have been proposed. The aim of these procedures is either to modify the substrate, eliminating “anchors” of reentry with linear lesions, or to target the focal triggers residing in the pulmonary veins in most of the cases. In patients with paroxysmal AF, electrical isolation of the pulmonary vein alone seems to be quite effective, although conclusive results are not yet reported.1,2 Conversely, in patients with permanent AF, especially if associated with valvular heart disease and left atrial dilatation, it is not clear which is the best ablative strategy.

In these latter patients, the most effective treatment available to date is surgical ablation. Starting with the Maze procedure, different surgical approaches have been proposed using different lesion schemes with variable success rates.3–12 What all the surgical design sets have in common is the fact that both the pulmonary veins and the posterior part of the left atrium are involved. This makes it difficult to know the relative contributions for the procedural clinical success of pulmonary vein isolation and linear left atrial lesions, respectively.

Up to now, no data comparing the clinical efficacy of the different surgical ablation schemes have been available. Furthermore, and more importantly, in the majority of the studies, the real electrophysiological effects of the surgical ablation achieved in the operating room have not been validated with an electrophysiological method to demonstrate the completeness and transmurality of the linear lesions or the complete isolation of the pulmonary veins in the case of the encircling procedure.

This study was performed to clarify the role of pulmonary vein isolation alone versus left atrial linear lesions localized in the posterior region in the treatment of permanent AF in the
setting of significant left atrial dilatation and valvular heart disease. The primary end point was to evaluate the persistence of sinus rhythm (SR) off antiarrhythmic drugs (AADs), correlating the clinical outcome with the surgical results validated with an electrophysiological study.

Methods

Study Sample

A total of 125 consecutive patients with permanent AF undergoing valvular operation were asked to undergo the additional cryoablation procedure. Of these, 105 patients agreed to proceed, whereas the remaining 20 patients declined. The study sample included 105 patients (mean age, 61 ± 10 years) with permanent AF (mean duration, 48 ± 51 months; range, 6 to 240 months). Written informed consent was required from all patients before surgery. Patients were assigned in a sequential fashion to 3 different surgical ablation schemes (Figure 1) according to a list of randomization established before the beginning of the study. Exclusion criteria included only the refusal of the patient, and no other criteria, such as left atrial dimensions, left ventricular ejection fraction, and duration of AF, were considered exclusion criteria. The primary end point of the procedure was the persistence of SR without AADs, and the secondary end point was the persistence of SR with the addition of AADs.

Thirty-five patients underwent a reversed “U” linear cryoablation interconnecting the pulmonary vein ostia and the right and left lower pulmonary veins down to the mitral annulus (MA) (group “U”), and 35 patients underwent a “7” linear cryoablation interconnecting the pulmonary vein ostia and the left lower pulmonary vein only down to the MA (group “7”). This scheme was different in comparison with the previous one with regard to the lack of the lesion connecting the right inferior pulmonary vein (RIPV) to the MA, and furthermore, it avoids a complete electrical isolation of the posterior region of the left atrium. In 35 patients, the ablation was limited to anatomic isolation of pulmonary veins performed just around the PV ostia (group “PV”).

Surgical Procedure and Cryoablation

All operations were performed under routine cardiopulmonary bypass with double venous cannulation and moderate hypothermia. The left atrium was opened through the usual left paraseptal incision after cold cardiopлегic arrest. After the mitral and/or aortic valves had been repaired or removed, cryoablation was started. The technique has been described elsewhere.11 The left appendage was ligated externally at this time in all the patients. Finally, a mitral or aortic prostheses was inserted if required, and the operation continued as usual.

Postoperative Management and Follow-Up

During hospitalization, all the patients were monitored by continuous ECG recordings. In the case of early AF recurrence, electrical cardioversion was performed during the hospital stay. AADs with oral amiodarone (200 mg/d, after loading dose), or propafenone (300 mg BID) in the case of a history of dysthyroidism, were administered routinely for the first 3 months and then withdrawn in the absence of AF recurrences. At time of electroanatomic mapping (EAM), direct-current cardioversion was performed to restore SR if AF was present. After discharge, the patients were followed up with clinical examination, ECG, and Holter monitoring at 3, 6, 9, 12, 18, and 24 months. In the case of symptom recurrence between follow-up visits, patients were followed up with clinical examination and ECG, and an event recorder was applied. In the case of AF recurrence after 3 months, AAD was reinitiated to assess the secondary end point. AF recurrences within the first 3 months after surgical operation were not considered in the statistical analysis, because AF recurrences in the early postoperative period may be a result of the surgical procedure per se. Therefore, the follow-up starts at the third month after surgical operation.

Doppler echocardiography with evaluation of transtricuspid and transmitral flow was performed before discharge and at 6 months after the operation. Cardiac magnetic resonance imaging was performed in the first 51 patients (17 for each group) to detect possible pulmonary vein stenosis.

After 6 months, if SR persisted, oral anticoagulant therapy was discontinued in patients in whom valve repair or bioprosthesis implantation was performed, and the presence of atrial contraction was documented by Doppler echocardiography.

Electrophysiological Study and EAM

The Institutional Review Board approved the study protocol, and the first 51 patients (17 for each group) underwent an electrophysiological study at 3-month follow-up after written informed consent had been obtained.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Group U</th>
<th>Group 7</th>
<th>Group PV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>14/21</td>
<td>15/20</td>
<td>12/23</td>
<td>0.59</td>
</tr>
<tr>
<td>Age, y</td>
<td>63±9</td>
<td>60±11</td>
<td>62±8</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean NYHA class</td>
<td>2.7±0.4</td>
<td>2.6±0.6</td>
<td>2.5±0.6</td>
<td>0.25</td>
</tr>
<tr>
<td>AF duration, y</td>
<td>51±36</td>
<td>48±32</td>
<td>47±35</td>
<td>0.80</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>52.9±6.4</td>
<td>51.3±7.3</td>
<td>50.7±5.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>0.84</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>0.84</td>
</tr>
<tr>
<td>Mitral stenosis and regurgitation</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>0.94</td>
</tr>
<tr>
<td>Aortic stenosis and/or regurgitation</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0.86</td>
</tr>
<tr>
<td>Mitral + aortic</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0.90</td>
</tr>
</tbody>
</table>
A nonfluoroscopic EAM system (CARTO, Biosense)\textsuperscript{13–15} was used to reconstruct the left atrium and to evaluate the atrial activation sequence and the lines of conduction block surgically created.

In patients in SR, the mapping procedure was performed during coronary sinus pacing at 600-ms cycle length. In the case of organized atrial arrhythmias (left atrial flutter), the electroanatomic reconstruction was performed during the arrhythmia, with the atrial electrogram recorded from the coronary sinus catheter used as reference. Both voltage and activation maps were performed in all patients except those in which the study was performed in AF \textsuperscript{2}; in this case, only the voltage map was performed.

Scar was defined as a site showing no atrial activity or having atrial electrograms with amplitude <0.05 mV. In addition, a complete conduction block across a scar area was arbitrarily defined if an inversion of activation wave front was noticed and an activation delay of at least 120 ms between 2 adjacent points encompassing the line of block was observed.

Validation of pulmonary vein isolation was performed by mapping the perimeter of the pulmonary vein ostium with a 4-mm-tip ablation catheter (NAVI-star, Biosense Webster) and mapping with multipolar ring catheters placed at the ostium of the pulmonary vein, with a Constellation catheter (Boston Scientific) used in the first cases and then the LASSO (Cordis Webster) catheter, when available. A complete electrical isolation of the pulmonary vein was considered if no or dissociated pulmonary vein potentials were present for the whole perimeter of the ostium or inside the vein itself, as previously described.\textsuperscript{1}

In addition, an angiogram of the 4 pulmonary veins was performed.

If atrial arrhythmias persisted at the end of the study, electrical cardioversion was attempted to restore SR. At discharge, pharmacological therapy was discontinued if the patient remained in stable SR regardless of the results of the EP study.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. Continuous variables were compared by use of a Student’s \( t \) test. Categorical variables were compared by Fisher exact test when appropriate or \( \chi^2 \) analysis. A Kaplan-Meier analysis\textsuperscript{16} with the log-rank test was used to determine the probability of freedom from recurrent AF. Results were considered to be statistically significant at a value of \( P<0.05 \). The software used was S-Plus 2000 (Math Inc).

**Results**

**Surgical Procedure and Early Postoperative Period**

No significant differences in the duration of aortic cross-clamping time and extracorporeal circulation in the 3 groups were observed. The mean time to complete the cryoablation in the 3 groups was 18±3, 15±4, and 14±4 minutes, respectively, for groups U, 7, and PV.

Perioperative death occurred in 3 patients (2.8%), 1 in each group. One patient died because of perioperative prosthesis valve thrombosis, and 1 patient with thrombophilic disease and previous thromboembolic events died because of massive pulmonary embolism after 6 days while in the rehabilitation ward. The third patient died of sepsis 30 days after the procedure. Four patients underwent a second operation before discharge because of bleeding in 2 patients and valvular leak in the other 2. One patient with mechanical mitral prosthesis had an ischemic stroke with no sequelae before the international normalized ratio value reached the therapeutic range.

No death was considered to be related to AF ablation, even if it occurred early after the operation. No complications clearly related to the ablation procedure occurred in any patient.

**Follow-Up**

The mean follow-up time was 41±17 months. Two patients died, one after 3 months because of heart failure and the second one of valvular endocarditis 15 months after the surgical procedure. Both patients were in AF and belonged to the U group.

The rhythm outcome in the total population divided into the 3 groups of patients showed that at 24 months, SR without AADs was present in 57% of group U patients, in 57% of group 7 patients, and in 20% of pulmonary vein isolation patients. The percentage of SR increased up to approximately 90% in groups U and 7 patients and up to 59% in pulmonary vein isolation patients with the addition of AADs.

At the end of follow-up, echocardiography showed the presence of atrial contractility in 72 of the 80 patients (90%) in SR.

**Clinical Results and Correlation With EAM**

The first 51 patients underwent cardiac MRI and electrophysiological study at 3-month follow-up. The EAM of the left atrium was accomplished with a mean of 115±22 acquisition points, with no differences among the 3 groups. A retrospective analysis showed no significant differences in terms of mean age, mean duration of AF, left atrial size, or type of valvular disease among these 3 groups of patients. Mean atrial volume evaluated with the 3D reconstruction was 150±40, 153±52, and 152±44 mL, respectively, in the 3 groups.

At the time of the study, the arrhythmia patterns of the 3 groups were as follows.

**Group U (17 Patients)**

Thirteen patients (76%) were in SR. Three patients (18%) showed left atrial tachycardia, in 1 case also associated with common atrial flutter, and 1 patient (6%) had paroxysmal AF.

The EAM showed that the complete U lesion scheme was not achieved in any patient. In all patients, the segment between the RIPV and the MA was missing. (Figure 2A).

In 10 patients (59%), the EAM showed a complete line of scar connecting the posterolateral MA and left inferior pulmonary vein (LIPV), left superior pulmonary vein (LSPV), right superior pulmonary vein (RSPV), and RIPV, thus creating a scar identical to the complete 7 scheme (Figure 2B). Of these 10 patients, 9 were in stable SR, whereas 1 showed SR alternating with paroxysms of typical and atypical atrial flutter.

The other 7 patients showed different patterns of incomplete lesion between the line connecting the RSPV with the LSPV in 2 patients and an incomplete lesion between the LIPV and the MA in 5. Among these 7 patients, 4 were in SR, 1 had AF, and 2 had left atrial tachycardia.

**Group 7 (17 Patients)**

Thirteen patients (76%) were in SR, 2 (12%) in left atrial tachycardia, and 2 (12%) in AF.

The EAM showed a complete 7-lesion scheme in 11 patients (65%) (Figure 2B); 9 of these 11 patients were in SR, 1 in paroxysmal AF, and 1 in paroxysmal left atrial tachycardia.

In the other 6 patients (35%), the surgically intended lesion was not achieved; the conduction gap was between the LIPV and the MA in 4 patients and between the RSPV and LSPV...
in 2 patients. Four of these 6 patients were in SR, 1 patient had permanent AF, and 1 patient showed permanent left atrial tachycardia.

**Group PV (17 Patients)**

Five patients (29%) were in SR, whereas 9 patients (53%) were in AF and 3 (18%) were in atypical atrial flutter.

The EAM and the PV ostia mapping with multipolar catheters showed complete isolation of the 4 pulmonary veins in 12 patients (71%) (Figure 2C). Three of these patients were in SR, whereas 7 were in permanent AF and 2 in permanent left atrial flutter.

In the other 5 patients (29%), the pulmonary vein potential was recordable in at least in 1 vein in each patient. Two patients were in SR, 1 patient in permanent left atrial flutter, and 2 patients in permanent AF.

Left atrial tachycardias were mapped during the EAM, and most of them were reentrant atrial tachycardias circulating through conduction gaps located along the ablation lines, especially around the MA. They were not ablated, but an electrical cardioversion was successfully attempted.

No pulmonary vein stenosis was detected at cardiac MRI.

**Two-Year Follow-Up: Clinical Results Correlated With the 3D EAM Findings**

Group U (17 patients): Of the 10 patients with a complete, although not aimed, 7 scheme, 9 (90%) were in SR without drugs, whereas the other 1 patient presented paroxysmal left atrial flutter. Among the other 7 patients without a complete 7 lesion, only 2 (28%) were in SR without AADs, whereas the other 5 needed AADs to maintain SR.
Of the 17 patients, SR was present in 11 (65%) without AADs, and with AADs, the number increased to 16 patients (94%) (Figure 3, A and B).

**Group 7 (17 Patients)**

Of the 11 patients who showed a complete 7 lesion, 9 patients (82%) were in SR without drugs, whereas 2 needed AADs to maintain SR. Among the other 6 patients with incomplete 7 lesion, 1 patient was in SR without AADs and 4 with AADs; 1 patient had paroxysmal left atrial tachycardia despite drug therapy.

Of the 17 patients, SR was present in 10 (59%) without AADs, whereas with AADs, the number increased to 16 patients (94%) (Figure 3, A and B).

**Group PV (17 Patients)**

Of the 12 patients with complete isolation of the 4 pulmonary veins, 3 patients (25%) were in SR without AADs, and the
number of patients increased to 7 (58%) with the addition of AADs. The other 5 patients showed AF in 4 cases and left atrial tachycardia in 1. Conversely, among the 5 patients without complete PV isolation, 3 patients were in SR with AADs, and 2 were in permanent AF.

Of the 17 patients, SR was present in 3 patients (18%) without AADs, and the number increased to 10 (59%) with the addition of AADs (Figure 3, A and B).

It is worth noting that if we consider the 21 patients in whom a complete 7 lesion was achieved, at 2-year follow-up, 18 patients (86%) were in SR without the addition of AADs, and the number increased to 20 patients (94%) with the addition of AADs. The only patient not in SR was in left atrial flutter. Conversely, among the 12 patients with complete pulmonary vein isolation, only 3 (25%) were in SR without AADs (Figure 3, A and B).

Discussion
The major findings deriving from the study are as follows.

1. The maintenance of SR off AADs during a long-term follow-up in patients with permanent AF associated with valvular heart disease was achieved in more than 85% of the patients when a complete linear lesion connecting the 4 pulmonary veins and the LIPV with the MA (7 scheme) was obtained.

2. Complete electrical isolation of the pulmonary veins alone is infrequently effective (25% success rate) in the same patient population.

3. An electrophysiological study to show what the surgeon really achieved in the operating room is essential to interpret correctly the clinical results in either a short- or a long-term follow-up, because a complete linear lesion or complete electrical pulmonary vein isolation is obtained in approximately 65% of patients with cryoenergy.

Curative nonpharmacological therapies are currently being developed both by surgeons and by interventional cardiologists. Previous studies showed the necessity of the simultaneous existence of several reentrant wavelets in a critical mass of atrial tissue for the maintenance of AF;17,18 and furthermore, the role of triggering foci for the initiation of AF has been well documented.19 Therefore, the therapeutic strategies of AF ablation proceed over different directions: elimination of the trigger or modification of the substrate, or both. Various ablative approaches, such as focus ablation, anatomic circumferential ablation, linear lesions, and debulking, have been proposed.1,6,9–12,19–22 There is no consensus, however, on which is the better strategy to treat AF, especially if the AF is permanent and associated with left atrial dilatation, as occurs in valvular heart disease.

Surgical experience has shown that regardless of the technique used (cut and sew, radiofrequency, or cryoenergy), ablation limited to the posterior part of the left atrium may be effective, with different percentages of success in eliminating AF. The results from these different series are not easily comparable, because different clinical end points were proposed and the use of AADs was not standardized.1–11 Furthermore, all the surgical ablation schemes proposed in recent years have in common the involvement of the posterior part of the left atrium and the pulmonary veins, and no study compared the efficacy of the different lesion schemes in the same series of patients. Therefore, it is still unknown which is the most effective design and, in particular, whether a complete posterior left atrium isolation is required or a more limited linear lesion is equally effective, or, finally, whether the pulmonary vein isolation alone is sufficient in the treatment of patients with permanent AF associated with valvular heart disease.5

A very important and still unresolved issue is the knowledge of the real electrophysiological effects of the surgical lesions. In only very few studies was an EAM performed to really assess the electrophysiological effects of the surgical ablation.12 In fact, performing the ablation procedure does not necessarily mean that completeness and transmurality of the lesions have been achieved. The electrophysiological validation may therefore permit a correct and meaningful evaluation of the clinical follow-up.

The results of the present study comparing electrical isolation of the pulmonary veins, linear lesions with posterior left atrium isolation (U scheme), and more limited linear ablation (7 scheme) validated with EAM showed that the clinical results attributed to an attempted U in reality must be attributed to a complete 7 lesion, because, at least endocardially, it was not possible to completely isolate the area between the RIPV and the MA. When achieved and electrophysiologically demonstrated, a linear lesion (7 scheme) connecting the pulmonary veins and the LIPV to the MA is effective in more than 85% of patients in restoring and maintaining SR in a long follow-up without the addition of AADs. Given the extremely high success rate of the 7 lesion, it seems that this scheme is a good compromise between atrial damage and clinical success; in addition, the 7 lesion allows the electrical activation of the posterior left atrium and subsequently a more physiological and global contraction, as shown by the fact that in 90% of patients, the echocardiogram showed a normal left atrial contractility. Similar results have been reported in a study that showed similar effectiveness of a similar surgical scheme in patients with persistent and paroxysmal AF not associated with valvular heart disease.

With regard to the clinical results of the pulmonary vein isolation, we noticed that this technique alone is effective in only 25% of patients, a percentage similar to the one observed in a previous study with patients affected by permanent AF and valvular heart disease who underwent cardiac valve surgery without cryoablation.11 Pulmonary vein isolation in the patient population studied is not as effective as the pulmonary vein ablation of idiopathic AF.1,11,21 It is likely that in our patient population, the electrical substrate plays a more important role than the focal firing from the pulmonary veins. In fact, in patients with long-standing valvular disease, the atrial enlargement with subsequent elongation and stretch of the fibers and fibrosis represents the substrate that may facilitate microreentry and fibrillatory conduction.23

The other important finding that clearly emerges from this study is the difficulty in obtaining linear, contiguous, and transmural lesions and a complete pulmonary vein isolation even in the operating room under direct vision, at least by use of cryoenergy. In fact, correlating the surgical results with
EAM findings, we found that the aimed surgical complete isolation of the posterior left atrium was never achieved, because the segment between the RIPV and the MA was always missing. These results might be explained by anatomic peculiarities, such as muscular bridges over the wall of the coronary sinus seen on the subepicardial surface, or the proximity of the valvular ring, the venous sinuses, and the arteries, making it difficult to achieve a transmural lesion with an endocardial approach. Conversely, even the aim of a complete linear lesion by performing the 7 scheme and the complete electrical isolation in the case of encircling of the PVs was achieved in only approximately two thirds of the patients.

This observation is extremely important, because clinical results during long-term follow-up can be misinterpreted, especially if the clinical success of the ablative procedure is considered together with the addition of AADs. In our series, the percentage of success without AADs was 65% in the total population, irrespective of the EAM results, but considering the patients in whom the linear lesions were really confirmed with the EAM, the percentage rises to 86%.

In patients in whom the surgical end point was not obtained, as shown by the EAM, the addition of pharmacological therapy made it possible to increase the percentage of patients in SR. This increase was not so evident when the percentage of success was already high with ablation, as in the case of linear lesions (from 86% to 94%), but the increment was very significant in the case of pulmonary vein isolation (from 25% to 60%). The necessity for AADs to maintain SR, although they determine a response during long-term follow-up can be misinterpreted, because no pulmonary vein stenosis was seen and no complications occurred in a long-term follow-up.

Conclusions

In patients with permanent AF and associated valvular heart disease, a limited approach involving linear lesions connecting the pulmonary veins and the LIPV to the MA is extremely effective in restoring and maintaining SR even in the long run. In this patient population, electrical pulmonary vein isolation alone is insufficiently effective. Given the high success rate and the relatively small amount of time added to surgery, cryoblation with a 7 linear scheme could be proposed in all patients with AF and valvular heart disease undergoing valve surgery.

References

Linear Cryoablation of the Left Atrium Versus Pulmonary Vein Cryoisolation in Patients With Permanent Atrial Fibrillation and Valvular Heart Disease: Correlation of Electroanatomic Mapping and Long-Term Clinical Results
Fiorenzo Gaita, Riccardo Riccardi, Domenico Caponi, Dipen Shah, Lucia Garberoglio, Laura Vivalda, Alessandro Dulio, Andrea Chiecchio, Eric Manasse and Roberto Gallotti

_Circulation_. 2005;111:136-142; originally published online December 27, 2004; doi: 10.1161/01.CIR.0000151310.00337.FA
_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/111/2/136

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/