Effect of Right Atrial Isthmus Ablation on the Occurrence of Atrial Fibrillation

Observations in Four Patient Groups Having Type I Atrial Flutter With or Without Associated Atrial Fibrillation

Ashish Nabar, MD; Luz-Maria Rodriguez, MD; Carl Timmermans, MD; Adri van den Dool, RN; Joep L.R.M. Smeets, MD; Hein J.J. Wellens, MD

Background—The goal of this study was to test the hypothesis that the occurrence of atrial fibrillation (AF), in at least some patients with coexisting type I atrial flutter (AFL), is based on macro-reentry around the tricuspid valve orifice, including the right atrial (RA) isthmus, by evaluation of AF recurrences after successful ablation of AFL.

Methods and Results—Eighty-two consecutive patients with type I AFL, with or without concomitant AF, underwent radiofrequency ablation (RFA) of the RA isthmus by an anatomical approach. The results were analyzed in 4 groups of patients: group 1 (only AFL; 29 patients), group 2 (AFL > AF; 22 patients), group 3 (AF > AFL; 15 patients), and group 4 (developing AFL while receiving class IC antiarrhythmic drug therapy for AF, the “class IC atrial flutter”; 16 patients). In all groups, RFA of type I AFL was performed with a high (≥93%) procedural success rate. In group 1, only 2 patients (8%) had AF after (18±14 months) AFL ablation. These figures were 38% (20±14 months) and 86% (13±8 months) in groups 2 and 3, respectively. Group 4 patients (4±2 months) had a 73% freedom of AF recurrences with continuation of the class IC agent.

Conclusions—The low incidence of new AF during long-term follow-up after RFA of type I AFL makes it unlikely that radiofrequency lesions promote the development of AF. The impact of isthmus ablation on AF recurrences differs according to the clinically predominant atrial arrhythmia and suggests a possible role of the RA isthmus in the occurrence of AF in some patients. Ablation of class IC atrial flutter in patients with therapy-resistant AF is a novel approach to management of this patient subset. Careful classification of AF patients plays a role in the selection of the site of ablation therapy. (Circulation. 1999;99:1441-1445.)

Key Words: atrial flutter ■ fibrillation ■ catheter ablation

Atrial flutter (AFL) and atrial fibrillation (AF), which are both intra-atrial reentrant arrhythmias with differing complexity in their activation pattern and mechanisms, are frequently seen to coexist in clinical practice. Long-term success of radiofrequency ablation (RFA) of AFL may be undone by the occurrence of AF, either preexisting or developing de novo. Few studies have evaluated the incidence of AF after successful RFA of type I AFL.1-3 We evaluated the hypothesis that at least in some patients with coexisting type I AFL, maintenance of AF might be based on macro-reentry around the tricuspid valve orifice, including the right atrial (RA) isthmus. We therefore evaluated the long-term occurrence of AF after successful RFA of the RA isthmus for type I AFL.

Methods

Study Population

Eighty-two consecutive patients with type I AFL, identified by negative flutter waves in the inferior leads and positive flutter waves in lead V1,4 who underwent RFA of the RA isthmus by an anatomical approach were included. All procedures were performed between November 1994 and April 1998. Patients having documentation of additional episodes of AF were also considered for RFA. The patient population was divided into 4 groups after careful review of the available ECGs and 24-hour Holter recordings. Group 1 consisted of patients who had documented episodes of AFL alone. Patients included in group 2 predominantly had episodes of AFL and 1 to 3 isolated episodes of AF; thus, AFL was their most frequently occurring arrhythmia. Patients included in group 3 had predominant documentation of AF. In these patients, 1 or 2 episodes of AFL were detected. Patients with therapy-resistant AF and no previous documentation of AFL but who developed AFL on oral class IC antiarrhythmic drug (AAD) (propafenone or flecainide) were placed in group 4. We called this new AFL the “class IC atrial flutter.” After a median treatment duration of 3 months (range, 2 to 8 months), class IC atrial flutter occurred. The characteristics of the 82 patients are summarized in Table 1. Every patient was symptomatic with intermittent palpitations despite AAD therapy. Coronary artery disease was the most common structural heart disease among patients in groups 1 (n=14), 2 (n=3), and 3 (n=2) and was considered an exclusion criterion for patients in group 4. Tachycardiomyopathy was diagnosed in 3 patients in group 1, 2 patients in group 3, and 1 patient each in groups 2 and 4. Six patients had previously undergone coronary bypass surgery (1 in

Received August 10, 1998; revision received December 1, 1998; accepted December 17, 1998.
From the Department of Cardiology, Academic Hospital Maastricht, Maastricht, the Netherlands.
Reprint requests to Luz-Maria Rodriguez, MD, Department of Cardiology, Academic Hospital Maastricht, P. Debyelaan 25, 6202 AZ, Postbus 5800, Maastricht, Netherlands. E-mail LM.Rodriguez@cardio.azm.nl
© 1999 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org
group 1, 2 in group 2, and 3 in group 3), whereas repair of an atrial septal defect (group 1) and Ebstein’s anomaly (group 4) was performed in 1 patient each. Fifteen patients (9 in group 1, 2 in group 2, 3 in group 3, and 1 in group 4) had left ventricular ejection fractions (LVEF) <50%. Compared with patients in other groups, patients in group 1 had a higher incidence ($P=0.002$) of structural heart disease, whereas patients in group 2 had a larger ($P=0.04$) mean left atrial area. Devices implanted before ablation included a pacemaker (n=4, 2 each in groups 1 and 3) and an atrioverter (Metrix 3020 device, InControl; n=3: 1 in group 3 and 2 in group 4). All patients in group 2 had paroxysmal AF, whereas a greater (9 of 15) or an equal (8 of 16) proportion of patients in groups 3 and 4, respectively, had chronic persistent AF.

### Electrophysiology Study and RFA

Informed written consent was obtained. In patients with frequent arrhythmia recurrences, AADs were continued. Bidirectional isthmus conduction and collision of dual wave fronts were demonstrated, and programmed atrial stimulation was performed to induce AFL. Anatomically guided linear ablation of the RA isthmus was performed with a 4-mm-tip (Cordis Webster) or an 8-mm-tip (EP Technology or Cerablate Plus Flutter, Osypka, Sulzer Medica) ablation catheter stabilized through a 8F long sheath (SAPL or SR0, Daig Corp). Radiofrequency pulses were delivered with the temperature preset to 55°C (Osypka HAT 300S) or 70°C (Stockert GmbH) for 90 seconds. Ablation of the posterior and/or septal isthmus was performed. Initially, noninducibility of AFL was considered a procedural success. Later, we sought to achieve isthmus conduction block, initially unidirectional (confirmed by coronary sinus [CS] pacing) and currently bidirectional, at the conclusion of every procedure. Procedural success was always confirmed under isoproterenol infusion (1 to 3 μg/min). A 24-hour Holter recording was made before discharge. At follow-up, patients in group 1 discontinued AADs, and patients in groups 2 and 3 received AAD therapy to prevent AF recurrences. Patients in group 4 continued either propafenone or flecainide. If the first procedure was not successful, repeated RFA was advised.

### Follow-Up

Follow-up was conducted at the arrhythmia clinic, initially at 8 weeks and subsequently at 3-month intervals. Patients with successful RFA of AFL were eligible for follow-up analysis. Holter recordings were made at 8 and 12 weeks and when symptoms were suggestive of an arrhythmia recurrence. Patients with a documented AFL recurrence underwent repeated RFA. Patients with recurrent AF were managed with AADs and/or nonpharmacological alternatives. Current symptom status of all patients was confirmed by telephone.

### Statistical Analysis

Results are expressed as mean±SD, median, and range. Mean values were compared by 1-way ANOVA, and the χ² test (or Fisher’s exact test) was used for testing homogeneity in contingency tables. Results were considered to be significant at the 5% critical level ($P<0.05$).

### Results

#### Electrophysiology Study and RFA Procedure

Results of electrophysiology study and RFA procedures in the 82 patients are summarized in Table 2. During the electrophysiology study, more patients in group 1 ($P=0.01$) presented with incessant AFL. One patient in group 1 and 3 patients in group 2 were successfully ablated after a second procedure. A second attempt failed to ablate AFL in 1 patient (group 3). The mean AFL cycle length in the 4 groups varied from 230±28 to 257±37 ms. Predominantly, a clockenosewise AFL was induced in all 4 groups. More ablation procedures were performed during CS pacing in patients from groups 1 through 4, whereas a preference for ablation performed during AFL was noted from groups 4 through 1 ($P=0.003$). Although statistically not significant, posterior RA isthmus was found to be most frequently ablated in the 4 study groups. However, a relatively greater percentage of patients in groups 2 through 4 required additional septal isthmus ablation. Successful RFA could be performed in ≥93% patients (93% in group 1, 96% in group 2, 93% in group 3, and 94% in group 4). A higher ($P=0.02$) mean number of radiofrequency pulses per successful procedure was required in group 4 patients (27±13) and was related to achieving a bidirectional isthmus conduction block in all successful procedures but 1 ($P=0.001$). One patient (group 3) developed complete AV block during septal isthmus ablation and needed a pacemaker. This patient had bidirectional isthmus conduction block and AFL noninducibility after the last RF pulse and was classified as a successful ablation.

#### Recurrence of AFL

Follow-up was available in all but 1 patient (n=76) after successful RFA of AFL (Table 3). Nine patients (12%) developed an AFL recurrence. No differences were noted ($P=NS$) in the recurrence rate of AFL in the 4 groups, and all AFL recurrences except 1 occurred within 6 months of ablation. In 7 patients, a recurrence after successful ablation was judged by either noninducibility (n=2 patients) or noninducibility and unidirectional isthmus conduction block (n=5 patients). In the latter 5 patients, there was a demonstrable isthmus conduction delay, indicating regression of isthmus conduction block (n=2 patients) or resumption of isthmus conduction (n=3 patients). The remaining 2 patients with bidirectional isthmus conduction block had resumption

---

### Table 1. Characteristics of the 82 Patients Divided Into the 4 Groups Studied*

<table>
<thead>
<tr>
<th>Group</th>
<th>(n=29)</th>
<th>(n=22)</th>
<th>(n=15)</th>
<th>(n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.5±15.5</td>
<td>55.9±16.4</td>
<td>50.8±15.7</td>
<td>53.7±13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>24/5</td>
<td>21/1</td>
<td>13/2</td>
<td>14/2</td>
<td>NS</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>18 (62)</td>
<td>5 (23)</td>
<td>4 (27)</td>
<td>2 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Median symptom duration, (range)</td>
<td>3 y (3 mo–10 y)</td>
<td>5.5 y (6 mo–30 y)</td>
<td>5 y (4 mo–13 y)</td>
<td>3.5 y (1 mo–20 y)</td>
<td></td>
</tr>
<tr>
<td>Failed AADs (median), n</td>
<td>2 (1–6)</td>
<td>3 (1–7)</td>
<td>3.5 (1–8)</td>
<td>3 (1–4)</td>
<td></td>
</tr>
<tr>
<td>Left atrial size, cm</td>
<td>4.4±0.5</td>
<td>4.7±0.8</td>
<td>4.2±0.4</td>
<td>4.6±0.3</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF &lt;50%, n</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>AF (paroxysmal/persistent), n</td>
<td>...</td>
<td>22/0</td>
<td>6/9</td>
<td>8/8</td>
<td></td>
</tr>
</tbody>
</table>

*Every patient had ≥1 documented episode of type I AF.
of isthmus conduction bidirectionally. After a repeated RFA requiring either 1 (n=7) or 2 (n=2) sessions, all patients are free of AFL recurrences at the long term.

**Atrial Fibrillation After RFA of Type I AFL**

The mean follow-up duration was as follows: group 1, 18±14 months; 2, 20±14 months; and 3, 31±8 months. Patients in group 4 had a significantly (P<0.001) shorter mean follow-up (4±2 months). Two patients in group 1 had episodes of paroxysmal AF during the postoperative period after coronary bypass surgery. No other patient in this group developed AF. In group 2, 13 of 21 patients (62%), including 10 patients in whom AADs were discontinued, were free of AF recurrences. Furthermore, in 5 patients (24%), AF recurrences were controlled better with AADs that previously failed. Thus, 86% patients in group 2 had long-term improvement of concomitant AF. The remaining 3 patients had frequent AF recurrences resistant to multiple AADs. One patient underwent AV nodal ablation with pacemaker implantation, another had a surgical Maze procedure, and the third continues to be symptomatic despite AADs. In contrast, only 2 patients (14%) in group 3 were free of AF recurrences after withdrawal of AAD treatment. In 6 patients (43%), control of AF was achieved by an AAD that had failed before the ablation. This means that 57% of patients in this group had easier control of AF recurrences after RFA of AFL. The remaining 6 patients remained symptomatic despite trials with different AADs (n=4 patients) and nonpharmacological methods (n=2 patients). After successful RFA of class IC atrial flutter and continuation of propafenone or flecainide, 11 patients (73%) in group 4 had no AF recurrences. Two patients had few short-lasting and well-tolerated AF recurrences confirmed by the episode log of the atrioverter. Thus, at a short-term follow-up, definite improvement occurred in 87% of the patients. When the 4 groups were compared for incidence of AF recurrences after RFA of AFL, patients in group 1 had significantly (P<0.01) less risk of AF recurrences.

Follow-up was available in all but 1 patient from group 1 in the subgroup of 15 patients with LVEF<50%. Three patients (0 in groups 1 and 4, 1 in group 2, and 2 in group 4) had AF recurrences. In comparison, 23 of 62 patients (37%) with LVEF≥50% had an AF recurrence (P=0.13).

**Discussion**

The study population consisted of 82 consecutive patients who underwent linear ablation of RA isthmus for type I AFL. Both the ablation protocol and the criteria of procedural success evolved during the study period between November 1994 and
April 1998. As shown by the longer duration of mean follow-up, a greater number of patients in groups 1 (AFL, no AF) and 2 (AFL > AF) were considered for RFA during our early experience. More patients in groups 3 (AF > AFL) and 4 (class IC atrial flutter) were offered an RFA procedure later; hence, a shorter mean follow-up was available.

Anatomically Guided RFA of Type I AFL
High procedural success rates (86% to 98%) have been reported after RA isthmus ablation for type I AFL.1–4,6–10 In the present study, RFA of AFL was successful in ≥93% of patients in all 4 groups. Initially, ablation procedures were performed during AFL, and noninducibility2,7–9 was accepted as a procedural success. Later, after the introduction of isthmus conduction block as a criterion, ablation procedures were performed during sinus rhythm with CS pacing.6 Therefore, in the present study, there was an increasing use of ablation procedures being performed during CS pacing from groups 1 through 4. This change in ablation protocol was related to later recruitment of patients in groups 3 and 4. In all groups, procedural success was more frequent after ablation of the posterior isthmus (50% to 67%) compared with septal isthmus ablation alone (≥10%). This may relate to the ease of achieving a stable catheter position at the posterior isthmus. Interestingly, a greater proportion of patients in groups 2 through 4, involving patients with concomitant AF, underwent an additional septal isthmus ablation. A potential benefit of ablating the septal isthmus in patients with concomitant AF could be modification of the posterior AV nodal input,11 resulting in a better ventricular rate control and therefore better tolerance of AFL recurrences. During ablation of the septal isthmus, 1 patient developed complete AV block and required a pacemaker. Single cases of this complication have been reported.10 It indicates the small but definite risk of RFA of the septal isthmus.

Recurrence of AFL
Nine of 76 patients (12%) had a recurrence of AFL. Most recurrences (n=7) were in patients in whom noninducibility alone or noninducibility with a unidirectional isthmus conduction block was considered as a success. Higher recurrences (10% to 55%) have been reported after noninducibility alone as a criterion for successful ablation.2,7–9 The recurrence rates are lower (6% to 9%) in patients with complete bidirectional isthmus conduction block compared with patients with a unidirectional isthmus conduction block or bidirectional isthmus conduction delay at the conclusion of a successful ablation.1,4,6,10 All but 1 recurrence of AFL occurred within the initial 6 months after ablation. This stresses the need for close follow-up in the months immediately after a successful ablation. Regression (n=2 patients) or complete disappearance (n=5 patients) of isthmus conduction block was demonstrated during a repeated study, as previously reported.1,6,10 Recently, a complete line of double potentials has been advocated as a new success criterion to avoid misinterpretation of isthmus conduction delay as block.12 A successful repeated RFA in all 9 patients resulted in long-term freedom from arrhythmia recurrences.

Outcome of AF After Successful RFA of Type I AFL
A variable number (8% to 30%) of patients have been reported to develop AF after RFA of AFL.2,3,8,9 In group 1, only 2 patients developed AF, both during the postoperative course of coronary bypass surgery. This finding does not support that in patients with AFL, an RA isthmus radiofrequency lesion could be proarrhythmic for the development of AF.

On the basis of our current understanding, at least 3 mechanisms could be responsible for clinical coexistence of type I AFL and AF in patients included in groups 2 and 3: (1) RA leading circle reentry (type I AFL) with atrial dissociation and AF in the left atrium8; (2) RA leading circle reentry (type I AFL), which becomes unstable and degenerates into multiple wavelets of AF14; or (3) temporal dissociation of AFL and AF, with a tendency for significant periods of organization along the trabeculated RA in a craniocaudal direction during AF.15 During the first 2 mechanisms, AF is secondary to a type I AFL circuit and consequently should cease after RA isthmus ablation, which interrupts the flutter circuit. In AF resulting from the third mechanism, we may speculate that ≥1 wave fronts propagating along the trabeculated RA would extinguish on encountering the RA isthmus ablation line. This may reduce the critical number of wavelets necessary to sustain AF, which then terminates. The extent of “organization” in paroxysmal versus chronic AF is controversial.15,16 The chance of reducing or eliminating AF recurrences after ablation of type I AFL is greater in patients with the initial 2 mechanisms as the basis for atrial arrhythmias and less in case of the third mechanism. RFA of the RA isthmus for type I AFL in combination with previously ineffective AAD therapy was found to result in longer arrhythmia-free intervals in a greater proportion of patients (86%) in group 2 (AFL > AF) compared with group 3 (57%) (AF > AFL). From the above reasoning, it is attractive to postulate that a greater proportion of patients in group 2 had coexisting AFL and AF mediated via the first 2 mechanisms and consequently derived larger clinical benefit. Undoubtedly, the electrophysiological basis of the interrelation between AF and AFL needs further elucidation. On the other hand, the explanation for our data may be simple because

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFL Recurrence, n (%)</td>
<td>6 (23)</td>
<td>0</td>
<td>1 (7)</td>
<td>2 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to Recurrence, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>5</td>
<td>...</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;6 mo</td>
<td>1</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Success criteria during first RFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NI</td>
<td>2</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NI+UIC block</td>
<td>4</td>
<td>...</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NI+BIG block</td>
<td>0</td>
<td>...</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Repeated RFA of AFL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 procedure</td>
<td>4</td>
<td>...</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2 procedures</td>
<td>2</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

*RFA of AFL was successful in 77 patients. Follow-up was available in all but 1 patient.
ablation of the RA isthmus interrupts a major pathway for impulse conduction between the left atrium and RA. This may affect the ability of AF to remain sustained. In summary, what seems certain is that the chance of lowering AF recurrences appears definitely higher in the subgroup of patients with AFL as the predominant clinical arrhythmia.

Patients included in group 4 (class IC atrial flutter) had AF that was nonresponsive to multiple AADs. Rate-dependent prolongation of the atrial refractory period by class IC agents effected an increase in the wavelength and facilitated the conversion of AF (multiple smaller reentry circuits) to AFL (a single macro reentrant loop).17 After an RA isthmus ablation and continuation of class IC therapy, 87% of patients either were symptom free or had only short-lasting, well-controlled AF recurrences. A similar successful “hybrid” therapy in patients who were treated primarily with amiodarone for AF was recently reported by Huang et al.18

A small subgroup (n=15, 18.2%) of our patients had LVEF <50%. After AFL ablation, 3 of 14 patients (in 1 patient, we have no follow-up) had AF recurrences. Paydak et al1 found that a history of spontaneous AF and LVEF <50% were significant independent predictors of AF after AFL ablation. When both characteristics were present, 74% of their patients had AF recurrences.3

Study Limitations
Our study population was classified into 4 groups on the basis of documentation of AFL alone or in combination with AF. The exact incidence of arrhythmia episodes, especially those which were asymptomatic, is not known and may have affected our classification. Although every procedure involved an RA isthmus ablation, the ablation protocol and the criteria for procedural success have changed over the study period in keeping with advances in our knowledge. A complete isthmus conduction block at the conclusion of a successful procedure was not obtained in all patients. This has obvious implications for analysis of arrhythmia recurrences.

Conclusions
RFA of type I AFL can be performed, regardless of concomitant AF, with a high primary success rate and low overall AF recurrences. A low incidence of new AF after RFA of type I AFL indicates that those radiofrequency lesions do not or rarely lead to development of AF. In patients with type I AFL as the predominant clinical arrhythmia, RA isthmus ablation reduces recurrences of AF over a long period of follow-up. This procedure is less successful in patients with AFL and more frequent episodes of AF. Patients with therapy-resistant AF who develop a type I AFL while receiving class IC therapy also seem to profit, showing a reduced incidence of AF recurrences after AFL ablation. Our findings contribute to the growing conviction to individualize the site and extent of RFA(s) in patients with AF.16,19 Our ultimate goal in RFA for AF should be to apply the interventions only to the site(s) resulting in the greatest amount of success and the least amount of damage to atrial function.

Acknowledgment
Dr Nabar is supported by Wijnand N. Pon Foundation, Leusden, the Netherlands.

References
Effect of Right Atrial Isthmus Ablation on the Occurrence of Atrial Fibrillation: Observations in Four Patient Groups Having Type I Atrial Flutter With or Without Associated Atrial Fibrillation
Ashish Nabar, Luz-Maria Rodriguez, Carl Timmermans, Adri van den Dool, Joep L. R. M. Smeets and Hein J. J. Wellens

_Circulation_. 1999;99:1441-1445
doi: 10.1161/01.CIR.99.11.1441

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/99/11/1441

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/