Localized Sources Maintaining Atrial Fibrillation Organized by Prior Ablation

Michel Haïssaguerre, MD; Mélèze Hocini, MD; Prashanthan Sanders, MBBS, PhD; Yoshihide Takahashi, MD; Martin Rotter, MD; Frederic Sacher, MD; Thomas Rostock, MD; Li-Fern Hsu, MBBS; Anders Jonsson, MD; Mark D. O’Neill, MBChB, DPhil; Pierre Bordachar, MD; Sylvain Reuter, MD; Raymond Roudaut, MD; Jacques Clémenty, MD; Pierre Jais, MD

Background—Endocardial mapping of localized sources driving atrial fibrillation (AF) in humans has not been reported. Methods and Results—Fifty patients with AF organized by prior pulmonary vein and linear ablation were studied. AF was considered organized if mapping during AF showed irregular but discrete atrial complexes exhibiting consistent activation sequences for >75% of the time using a 20-pole catheter with 5 radiating spines covering 3.5-cm diameter or sequential conventional mapping. A site or region centrifugally activating the remaining atrial tissue defined a source. During AF with a cycle length of 211±32 ms, activation mapping identified 1 to 3 sources at the origin of atrial wavefronts in 38 patients (76%) predominantly in the left atrium, including the coronary sinus region. Electrograms at the earliest area varied from discrete centrifugal activation to an activity spanning 75% to 100% of the cycle length in 42% of cases, the latter indicating complex local conduction or a reentrant circuit. A gradient of cycle length (>20 ms) to the surrounding atrium was observed in 28%. Local radiofrequency ablation prolonged AF cycle length by 28±22 ms and either terminated AF or changed activation sequence to another organized rhythm. In 4 patients, the driving source was isolated, surrounded by the atrium in sinus rhythm, and still firing at high frequency (228±31 ms) either permanently or in bursts.

Conclusions—AF associated with consistent atrial activation sequences after prior ablation emanates mostly from localized sources that can be mapped and ablated. Some sources harbor electrograms suggesting the presence of localized reentry.

(Circulation. 2006;113:616-625.)

Key Words: ablation ■ arrhythmia ■ atrial flutter ■ mapping ■ tachyarrhythmias

Clinical Perspective p 625

Methods

Study Population

The study comprised 50 consecutive patients with organized AF occurring after prior ablation, including pulmonary vein (PV) isolation, cavotricuspid isthmus ablation, and left atrial (LA) linear ablation in the majority (at the LA roof joining the 2 superior PVs and/or the isthmus between the left inferior PV and mitral annulus). Organized AF was defined by endocardial mapping during AF displaying (1) irregular atrial cycle with beat-to-beat variations of ≥20 ms; (2) dominantly discrete atrial complexes with a consistent activation sequence for >75% of the time using catheters sequentially positioned at the right free wall, left anterior wall, and the coronary sinus (CS); and (3) the stability of activation evaluated over a 10-minute period of spontaneous or induced AF.

These patients represented 17% of 295 patients with persistent or recurrent AF after prior ablation. The procedural end point for the above ablation was electrical isolation of the PV and linear conduction block.
All patients gave written informed consent to participate in the study, which involved the use of an investigational catheter for mapping, and the protocol was approved by the institutional Clinical Research and Ethics Committee.

**Electrophysiological Study**
All antiarrhythmics, except for amiodarone (n=10), were ceased ≥5 half-lives before ablation. Oral anticoagulation was administered (target international normalized ratio, 2 to 3) for at least 1 month before the procedure, and transesophageal echocardiography was performed within 5 days of the procedure to exclude atrial thrombus.

Surface ECG and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Bard Electrophysiology). Intracardiac electrograms were filtered from 30 to 500 Hz.

The following catheters were introduced via the right femoral vein for electrophysiological study: (1) A steerable quadripolar catheter (5-mm electrode spacing, Xtrem, ELA Medical) was positioned as a reference in the right or left appendage or within the CS with the proximal electrode positioned at 4 to 5 o’clock along the mitral annulus in the left anterior oblique projection; (2) a 20-pole steerable mapping catheter arranged in 5 soft radiating spines (1-mm electrodes separated by 4-, 4-, and 4-mm interelectrode spacing) covering a diameter of 3.5 cm (PentaRay, Biosense-Webster) was introduced via a long sheath (Preface Multipurpose, Biosense-Webster) that was continuously perfused with heparinized glucose and left in the LA or right atrium; and (3) an irrigated-tip quadripolar ablation catheter with a distal 3.5-mm tip and then three 1-mm electrodes separated by 2, 5, and 2 mm (Thermocool, Biosense-Webster) also was used. After transseptal puncture, a single bolus of 50 IU/kg heparin was administered and repeated only for procedures lasting ≥4 hours.

**Study Protocol**
In all patients, an initial evaluation was performed of the PVs to determine the presence of conduction recovery. If PV-LA conduction was present, isolation was performed. In patients in sinus rhythm, linear lesions were evaluated and reablated if required.

**Mapping of AF**
Activation mapping was performed during organized AF to identify potential sources maintaining AF. The term “source” is used in a broad sense to indicate the origin of atrial wavefronts during AF without inferring its mechanism (focal or reentrant) or size (discrete or wide). A source was localized by step-by-step evaluation of atrial activation. The 20-pole catheter was used to identify the direction of activation by comparing the precocity of electrograms of the 5 limbs during AF relative to the reference electrogram (Figures 1 and 2A). The catheter was moved gradually in the direction of earliest activity until a site showing the earliest possible activity or an area centrifugally propagating to the surrounding atria was reached. An attempt was made to localize the source at the center of mapping field to obtain activation spreading from internal to external bipoles (Figure 2A, left). It was sometimes necessary to examine the order of activities during the longest atrial cycles to confirm their sequence. The lateral parts of the LA (facing the transseptal access) were easily mapped by the multilimb catheter, whereas the medial and septal parts required a 90° to 180° curvature, and sometimes all the spines could not be applied to the endocardial tissue simultaneously. When the sources originated from the most inferior part of the atria, signified by an inferior-to-superior direction of atrial activation, the multilimb catheter could not reach or stabilize along the tricuspid and mitral annuli and was replaced by the quadripolar ablation catheter. The latter was dragged along the endocardial inferior LA by looping the catheter to be positioned parallel to the CS catheter.

**Analysis of Electrograms at the Earliest Site**
The percentage of AF cycle length covered by an electrical activity at the earliest site was determined by adding the duration of all asynchronous electrograms and was expressed as a function of the mean AF cycle length duration. The cycle length of the source was calculated by averaging 10 consecutive cycles having an identical activation sequence. A frequency gradient around the atrial source was considered to be present if the surrounding LA had a ≥20-ms-longer cycle length demonstrated within the 20-pole mapping field. A frequency gradient in the CS region was evaluated by comparing local CS cycles and adjacent inferior LA (≈2 cm around using quadripolar catheters). In addition, the electrograms at the earliest site recorded by the ablation catheter were analyzed during the 4 seconds before ablation to evaluate the following characteristics: electrogram morphology separated into consistent (similar complexes) or inconsistent (varying complexes); electrogram duration measured from the beginning to end of the local electrogram averaged over 10 consecutive complexes and at the shortest and
longest cycle lengths; and if the proximal bipole had adequate tissue contact at the ablation site, the relative activation timing between distal and proximal bipoles (from electrogram onset to onset) separated into 3 categories (Figure 2B) as synchronous activation, distal-to-proximal activation (proximal electrogram starting before the end of distal one), or alternating activation (no overlapping between the distal and proximal electrograms).

**Inducibility of AF**

AF inducibility was evaluated by burst atrial pacing (5-second bursts at an output of 20 mA and a pulse width of 2 ms) from the mid CS and the right atrial and LA appendage (in random order), beginning at a cycle length of 250 ms and reducing at 10-ms intervals until atrial refractoriness. AF was considered inducible if it persisted for ≥10 minutes. If AF terminated after <10 minutes, induction was repeated at least 3 times from each of the 3 sites.

AF was defined by the beat-to-beat variability in cycle length, in contrast to atrial tachycardia, which was defined as a rapid regular atrial rhythm with stable cycle length, morphology, and activation sequence. A macroreentrant mechanism was defined by recording of the entire cycle length of activity in 1 chamber, with entrainment at ≥2 points (separated by ≥2 cm) demonstrating a postpacing interval <20 ms longer than the tachycardia cycle length.

The AF cycle length was determined within the CS or LA appendage before ablation by averaging 30 consecutive cycles using automated cycle length monitoring software (Bard Electrophysiology). Interelectrogram intervals of <100 ms were counted as a single interval. At each time point, the automated annotation was manually verified and corrected with online calipers at a paper speed of 100 mm/s.

**Radiofrequency Ablation**

Radiofrequency (RF) energy was delivered with a power of 35 W in the atrial tissue using irrigation rates of 5 to 60 mL/min (0.9% saline via Cool Flow; Biosense-Webster) for a duration of 60 to 240 seconds at the site or area of earliest activity. The multispine catheter was left in position throughout the ablation procedure if it was stable and was withdrawn if unstable. RF energy was delivered with a power of 25 to 30 W along the venous structures using multiple applications. Temperature was limited to 50°C. Successful ablation of the source was demonstrated by the termination of AF to sinus rhythm or a change in cycle length and activation sequence (conversion to another rhythm).
Follow-Up
After ablation, patients received subcutaneous heparin while oral anticoagulation was reinitiated. All patients had at least 3 days of ambulatory monitoring in hospital during this time. Amiodarone was ceased in all patients. Other antiarrhythmic drugs were ceased in paroxysmal AF and continued for 1 to 2 months in persistent AF.

Patients were hospitalized for 1 day at 1, 3, 6, and 12 months after the last procedure for assessment, including transthoracic echocardiography and ambulatory monitoring. Stress testing was performed at 3 months. At 12 months, all patients underwent CT angiography to exclude PV stenosis. If patients maintained sinus rhythm for 3 months, cessation of anticoagulation was considered. In the event of recurrence of AF or ectopy, patients were offered further ablation or trial of antiarrhythmics. A successful outcome was defined as the absence of arrhythmia (AF or flutter) beyond the second month.

Statistical Analysis
All variables are reported as mean ± SD. Comparison between groups was performed with the Student t test or the Wilcoxon signed-rank test. Statistical significance was established at P<0.05.

Results
Mapping during organized AF showed temporally stable and consistent activation sequence emanating from a localized site/area in 38 patients, whereas in 12 patients, AF became disorganized (inconsistent activation sequences) during mapping. Characteristics of these 38 patients are presented in the Table. The mean AF cycle length measured in the CS was 211±32 ms.

AF was mapped during the index procedure after PV and linear ablation in 15 patients; prior AF ablation was per-
Entrainment maneuvers could not be performed because of cycle length variations during AF. In 13 CS region sources, the earliest discrete activity could be identified at the rim of CS ostium in 2 or within the CS with a later activation of the immediately proximal and distal CS in 6 (Figure 5); in 5, the activation origin was inferred to originate from the initial 3 cm of the CS on the basis of later activation of all surrounding areas (septum, inferior LA, and distal CS). In the latter cases, a discrete early activation could not be identified because contiguous endocardial and epicardial sites showed alternating earliest activity, with rapid bursts resulting in an uninterrupted electrical activity in this region. The mean, shortest, and longest cycle lengths of the source were 196±47, 165±44, and 226±46 ms, varying by 59±37 ms at each individual location. There was 1:1 propagation from the source to the surrounding atrium in 35, whereas there was a gradient frequency >20 ms (44±27 ms) in 14 cases (28%; Figure 6). The cycle length was shorter at sites displaying a frequency gradient than in those with 1/1 propagation; mean cycle length was 165±39 versus 210±38 ms (P=0.0015), and shortest cycle length was 126±21 versus 179±39 ms (P<0.0001). There was no significant difference in the cycle length of sources located within the CS region and those at other atrial sites.

At the ablation site, the electrograms showed a consistent morphology in all but 3 cases. Their mean duration was 76±40 ms (range, 25 to 200 ms), prolonged at shortest AF cycle lengths (97±34 ms; P=0.0015), and shortened at the longest cycle lengths (48±17 ms; P=0.0015). The mean electrogram duration was >100 ms in 10 locations (20%).

Simultaneous distal and proximal (at 5-mm distance) recordings were available in 38 cases at the ablation site. The distal recording preceded proximal activity in 18, was synchronous in 4, and demonstrated a gradient in activation time, producing an alternate distal/proximal activity in 16 (42%).

Patients taking amiodarone had a longer initial AF cycle length than patients without amiodarone (215±51 versus 194±36 ms; P=0.06) but no difference in electrogram duration at the source origin.

**RF Ablation**

RF delivery resulted in termination of AF (Figure 7) or conversion to a new arrhythmia associated with a different activation sequence (Figure 4) confirmed to be due to another source or macroreentry. Conversion to AF originating from another source was associated with a 31±16-ms increase in cycle length.

For atrial sources, the duration of RF application to achieve termination or conversion of AF was 97±90 seconds (median, 60 seconds; range, 5 to 360 seconds). A single patient with multifocal ectopy from an LA appendage required multiple RF applications (up to 360 seconds), which resulted in inadvertent disconnection of the appendage. Atrial sources originating from the roof were adjacent to a prior ablation line in 4 of 5 patients.
CS sources were initially approached from the endocardial inferior LA in 6 patients (including the 5 without discrete early activation) by dragging along the mitral annulus. The delivery of 5±2 minutes of RF energy resulted in slowing of CS activity in 5 and local abolition of CS potentials in 1 (Figure 8); AF terminated to sinus rhythm in 2 patients (within 3 minutes of RF) and persisted in 4 patients. Ablation was begun within the CS in the remaining 7 patients; in the abovementioned 4, it followed unsuccessful endocardial ablation. Ablation limited to the ostium in 2 patients resulted in AF termination in <1 minute. In 9 patients, RF was delivered within the first 3 cm of the CS and resulted in arrhythmia termination: within 1 minute in 4 patients and after more prolonged applications (up to 5 minutes) in 5 patients. The mean duration of RF application to achieve termination or conversion of AF was 106±81 seconds (median, 60 seconds; range, 5 to 300 seconds). CS angiogram after ablation showed a diameter of <5 mm in 1 of 8 patients.

In the whole group, before termination, RF ablation resulted in an increase in AF cycle length of 28±22 ms. In 14 cases, the termination of AF was “heralded” by an abrupt slowing (pauses >300 ms) in LA activity during the last 30 seconds. In 4 patients, RF ablation organized AF to a regular atrial tachycardia (originating from the same location) before termination. During ablation, there was a single instance (at CS ostium) of sudden bradycardia of >3 seconds, indicating a vagal effect. The total RF delivery per location was 5±2 minutes (range, 1 to 8 minutes). The total fluoroscopic and procedural durations were 62±28 and 212±88 minutes, respectively.

Additional Ablation
A total of 5 patients had spontaneous conversion to macroreentrant flutter after elimination of a single source, and an additional 7 patients had inducible sustained flutter. Of these

Figure 6. Gradient of high-frequency activity recorded in the posterior LA. In both, the bipole A3–4 demonstrates the most rapid activity. Left, Activity at bipole A3–4 has a mean cycle length of 126 ms; the immediately surrounding bipoles are much slower, with a mean cycle length of 214 ms. Right, The activity in A3–4 is faster and/or split with the surrounding local activity having a cycle length of 144 ms.

Figure 7. Centrifugal activation recorded on the multispine catheter at the top of posterior LA (fluoroscopic image on the right bottom), with spine C demonstrating the earliest activity (*) in AF that had been sustained for 32 minutes. Right top, Ablation at this site with termination of AF 10 seconds after the beginning of ablation.
12, 6 had undergone no prior linear ablation, and 6 had a single prior line. Mapping demonstrated macroreentry around the right PVs (n=5), perimitrally (n=6), or a combination of both (n=1). They underwent RF ablation of the roof, mitral isthmus, or both, respectively.

There were 2 adverse effects: dissociation of LA appendage activity and a cerebral vascular accident 3 hours after the ablation procedure in another patient. At the end of the procedure, AF or atrial flutter was not inducible in 31 patients (82%), whereas 7 patients had inducible AF that displayed complex activation sequences and electrograms.

**Isolated Focal Sources**

In 4 patients, the area containing the source was inadvertently isolated, being recorded in a discrete point in 2 (1 each in the anterior LA and posterior LA) and along 2 adjacent bipoles in 2 (LA roof and CS). These islands were contiguous with either prior linear ablation in 3 or a surgical atriotomy in 1. The isolated area was surrounded by atrial tissue in sinus rhythm and showed persistent fibrillatory activity with a local cycle length of 228±31 ms (varying from 110 to 270 ms). The local activity within these fibrillating regions showed discrete electrograms in 3 or prolonged and alternating fractionated complexes in 1 (Figure 9). The isolated sources fired continuously in 2 patients and in bursts lasting 2 to 15 seconds in 2. In patients with continuous activity, the source abruptly ceased firing 8 minutes after isolation in 1 (and could not be reproduced by local pacing), whereas firing persisted in 1 case when remapped 5 days later.

**Follow-Up**

Early after ablation, 4 patients had recurrent AF or atrial flutter. Ablation was performed for foci triggering AF (1 in the superior vena cava and 1 in the CS ostium), recovery of PV conduction in 3, and a gap in the LA line in 1.

At 8±3 months of follow-up, 31 patients (82%) were arrhythmia free, including 26 without the use of antiarrhythmics. No patient, including those with CS ablation, developed clinical symptoms of coronary artery disease or ischemic features during exercise test 3 months after ablation.

**Discussion**

This study demonstrates that AF organized by prior ablation and associated with consistent atrial activation sequences is maintained predominantly by localized sources that can be mapped and ablated. Such sources demonstrate heterogeneous electrophysiological characteristics and varied from discrete early activity to complex local activity spanning most of the cycle length, suggesting different underlying mechanisms.

**Mapping of Sources Maintaining AF**

Patients were selected on the basis of organized AF displaying discrete electrograms and with a consistent activation sequence. These patients represented 17% of our patients with persistent or recurrent AF after prior ablation. Sources were identified by mapping atrial activation to localize the area with centrifugal propagation spreading to the surrounding atrium. This could be evidenced by either simultaneous local high-density multielectrode mapping or sequential conventional mapping. Their role in maintaining AF was confirmed by prolongation of the AF cycle length and a change in atrial activation sequence or AF termination during RF delivery.

The sources were observed to discharge continuously or in bursts and demonstrated varying cycle lengths. Their intrinsic properties were strikingly evidenced independently of external influence in patients with islands of fibrillatory activity isolated by ablation. Driving sources with such a spectrum of spontaneous activity maintaining AF have not been described previously in humans.

Although the exact arrhythmia mechanism could not be ascertained from the clinical electrophysiological data, the electrogram recordings indicate that some sources were discrete foci spreading rapidly from the internal to external
electrodes within the mapping field, whereas in 42% of cases, local reentry was suggested by prolonged electrograms spanning most of the cycle length or by alternating activation at adjacent sites. The latter observation indicates the presence of a local intervening arc of block; however, we could not distinguish whether this activation gradient resulted from asynchronous independent wavefronts or sequential activation of rotating waves. A rotating wave would be compatible with prior mapping studies of leading circle reentry in the rabbit or rotors in sheep, which reported wavelengths of 6 to 8 mm and 10 ± 3 mm, respectively, both of which should be identifiable within the spatial resolution of the presently used electrode spacing. Similar electrograms using the same high-density catheter during atrial tachycardia after AF ablation have been demonstrated with entrainment supporting a small circuit or rotor.

Stable sources as a mechanism maintaining AF have been reported in few studies compared with the large amount of literature demonstrating the role of wandering wavelets or closed-loop reentry. Either automatic foci or small rapid circuits (rotors) have been reported during acetylcholine-induced AF, in chronic pacing-induced AF, and in computer simulation models of AF.

Anatomic Location of Sources
In our patients, sources maintaining AF were widely distributed in the LA with some clustering along the CS–LA interface, the anterior LA, and the LA appendage; these
regions were distinct from those commonly involved in ablation strategies. The clustering at anatomic regions of structural discontinuities suggests the arrhythmogenic role of heterogeneous fiber properties favoring anatomic reentry or anchoring rotors or the uninterrupted interaction between contiguous structures to maintain AF, notably along the CS. In humans, intraoperative mapping studies that were spatially constrained by epicardial access have provided data indicating a localized substrate maintaining AF. Rapid repetitive activations were identified from the PV, the region lateral to the left PV, the “corners” of the posterior LA, the LA appendage, the CS, and occasionally the lateral right atrium.

Clinical Implications
The present study supports the notion that ectopic sources have an important role in the maintenance of AF, in addition to the PV and wavelets/reentrant loops. These sources are responsible in part for recurrent AF occurring after PV isolation and complete linear lesions, with their ablation being the last necessary step of substrate elimination, confirmed by the noninducibility of arrhythmia and clinical outcome in most patients.

Converging on the origin of atrial activation provided important information for their recognition. Prolonged or alternating (in contiguous electrodes) electrograms covering most of the cycle length may correspond to localized circuit or rotor. In some cases, the source harbored localized high-frequency potentials; in most, 1/1 atrial propagation rendered activation mapping indispensable in localizing the origin of wavefronts, highlighting the complementary role of techniques using frequency or activation mapping.

Study Limitations
In this cohort, mapping was facilitated by prior ablation, resulting in a relatively stable atrial activation and allowing identification of the earliest site. Whether a similar phenomenon could be identified in more complex forms of AF in the broader AF population is unknown. However, the method described based on identifying epochs of centrifugal activation provides a paradigm applicable to these conditions, possibly assisted by 3D signal analysis techniques and means to organize AF.

The information from local electrograms at the site of activation origin could not be evaluated in terms of specificity or predictive value for ablation. In addition, some of the complex signals may have resulted from prior ablation.

Finally, the safety of these procedures may be a concern, particularly when repeated ablation is required within the CS. In this series, there were no instance of hemopericardium, CS thrombosis, or clinically apparent side effects on the circumflex artery; however, the long-term impact of such ablation is unknown. In the patient in whom the left appendage was isolated, long-term anticoagulation is probably mandatory.

Acknowledgments
Dr Sanders is supported by the Neil Hamilton Fairley Fellowship from the National Health and Medical Research Council of Australia and the Ralph Reader Fellowship from the National Heart Foundation of Australia. Dr Rotter is supported by the Swiss National Foundation for Scientific Research, Bern, Switzerland. Dr Rostock is supported by the German Cardiac Society. Dr Jonsson is supported by the Swedish Cardiac Society. Dr O’Neill is supported by the British Heart Foundation.

Disclosures
PentaRay catheters were developed and provided by Biosense-Webster, Drs Sanders, Jais, and Haissaguerre report having served on the advisory boards of and having received lecture fees from Biosense-Webster and Bard Electrophysiology. Drs Rotter and Hsu report having received lecture fees from Biosense-Webster. The other authors report no conflicts.

References
The most widely accepted mechanism for the maintenance of AF has been multiple reentrant wavelets or loops. However, it is being increasingly suggested that localized sources of activity may have a role in the maintenance of AF. To date, direct mapping evidence of a localized source has been demonstrated only in experimental models. This clinical study demonstrates that after AF became organized (by ablation around PVs and selected other sites), further mapping could identify localized sources maintaining AF where ablation then terminated AF. These sources were characterized as discrete foci or areas of small reentrant activity (potentially “rotors”). It is hoped that recognition and ablation of localized sources may lead to further improvement in the success of AF ablation, particularly in patients with chronic AF.
Localized Sources Maintaining Atrial Fibrillation Organized by Prior Ablation
Michel Haïssaguerre, Mélèze Hocini, Prashanthan Sanders, Yoshihide Takahashi, Martin Rotter, Frederic Sacher, Thomas Rostock, Li-Fern Hsu, Anders Jonsson, Mark D. O'Neill, Pierre Bordachar, Sylvain Reuter, Raymond Roudaut, Jacques Clémenty and Pierre Jaïs

Circulation. 2006;113:616-625
doi: 10.1161/CIRCULATIONAHA.105.546648
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 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/113/5/616

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/