BioSTAR Evaluation STudy (BEST)

A Prospective, Multicenter, Phase I Clinical Trial to Evaluate the Feasibility, Efficacy, and Safety of the BioSTAR Bioabsorbable Septal Repair Implant for the Closure of Atrial-Level Shunts

Michael J. Mullen, MB, BS, MRCP, MD; David Hildick-Smith, MD, MRCP; Joseph V. De Giovanni, MD, FRCR, FRCPCH, MOM; Christopher Duke, MB, ChB, MA, MRCP; W. Stewart Hillis, MB, ChB, FRCR, FRCS; W. Lindsay Morrison, MD, FRCP; Christian Jux, MD

Background—The use of permanent synthetic implants to close atrial septal defects (ASD) and patent foramen ovale (PFO) has a number of limitations, including late complications and the limiting of transeptal access to the left heart should it be required for the later treatment of acquired heart disease. BioSTAR is a novel, bioabsorbable, atrial septal repair implant. This phase I pilot study evaluates the feasibility, safety, and effectiveness of BioSTAR for the first time in humans.

Methods and Results—We conducted a prospective, open-label, multicenter clinical study in 58 patients aged 28 to 68 years who had a clinically significant ASD or PFO. Percutaneous shunt closure was undertaken with the BioSTAR septal repair implant. Successful device implantation was achieved in 57 (98%) of 58 patients. Closure at 30 days and 6 months, assessed by contrast transthoracic echocardiography, was 48 (92%) of 52 and 54 (96%) of 56, respectively. There was no evidence of a clinically significant response to the device. Transient atrial arrhythmia occurred in 5 patients after implantation. No major safety issues were observed.

Conclusions—This study demonstrates the feasibility, safety, and effectiveness of BioSTAR for the closure of ASD and PFO in humans with a high rate of early and complete shunt closure. BioSTAR is a novel septal repair implant designed to provide biological closure of atrial-level defects using the patient’s natural healing response. Because 90% to 95% of the implant is absorbed and replaced with healthy native tissue, future access to the left atrium may be achieved. (Circulation. 2006;114:1962-1967.)

Key Words: heart septal defects ■ heart defects, congenital ■ pediatrics ■ stroke

Atrial-level shunts, such as atrial septal defect (ASD) and patent foramen ovale (PFO), are common congenital cardiac defects.1,2 The increasing recognition of the long-term complications that arise from atrial level shunts, including right heart volume overload, paradoxical embolism, cyanosis, decompression illness, and migraine, means that in many cases, closure of the defect is recommended, often at a young age. In the majority of cases, this can now be achieved by percutaneous transcatheter placement of a permanent synthetic implant to occlude the defect through a combination of mechanical closure and fibrous encapsulation of the device.3-6 This process is not always fully achieved, and residual leaks are common after implantation.4,5,7 In addition, late complications, including arrhythmia,8-11 erosions,12-14 thrombus formation,15 and allergic reactions, have been reported.16,17

Clinical Perspective p 1967

Long-term follow-up of these permanent implants remains limited, and the potential for late unexpected complications remains long after the defect is effectively sealed and the device function has become redundant. Furthermore, it has recently been reported that a persistent low-grade inflammatory response to such devices persists for many years after implantation and might result in late and unexpected complications.18 In addition, a permanent synthetic device will obstruct access to the left atrium that might be necessary for the later treatment of acquired heart disease. The development of an absorbable device that utilizes endogenous healing to effect a rapid and complete sealing of the defect, before being absorbed and replaced by host tissue, is therefore both
intuitively attractive and offers the potential for long-term benefit.

The BioSTAR septal repair implant (NMT Medical, Boston, Mass) is a novel, bioabsorbable device specifically designed for the closure of ASD and PFO. BioSTAR uses an acellular porcine intestinal collagen layer (ICL) matrix (Organogenesis, Canton, Mass), mounted on an MP3SN STARFlex (NMT Medical) “double-umbrella” framework (Figure 1).3,19–21 The device is coated with a heparin benzalkonium chloride complex (Celsius, Cincinnati, Ohio), which in animal experiments reduced protein and blood cell deposition and thrombus formation.22 BioSTAR has a self-centering mechanism that consists of nitinol microsprings connected between the left and right atrial umbrellas (Figure 1). The collagen matrix is rapidly incorporated into the atrial septum, which results in a low profile and early sealing of the defect.22,23 Gradual remodeling occurs over a period of ≈24 months, during which the collagen is absorbed and replaced by host tissue.22,23 The BioSTAR Evaluation STudy (BEST) was designed to assess for the first time in humans the feasibility, safety, and efficacy of the BioSTAR septal occluder in the closure of PFO and ASD.

Methods
BEST was a prospective, nonrandomized, multicenter, single-arm study conducted in the United Kingdom. The study protocol was approved by the West Midlands Multicenter Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency. All patients gave written informed consent. Patients were included in the study if they were aged 18 years or over and had a clinically significant atrial-level shunt. Indications for closure of PFO included cryptogenic stroke, decompression illness, and orthodeoxia platypnea. Centrally located atrial septal defects with an adequate rim were considered clinically significant and included if the right heart was dilated. Patients with other congenital or significant acquired cardiac defects, a previous septal implant, known thrombophilic disorder, or a history of heparin-induced thrombocytopenia were excluded from the study.

Implantation Procedure
Procedures were performed with patients under general anesthesia with fluoroscopic and transesophageal echocardiography (TEE) imaging. Before the procedure, patients were preloaded with aspirin 300 mg and clopidogrel 300 mg. The morphology and excursion of the intra-atrial septum was initially assessed with TEE. An aneurysm was defined as total excursion of ≥15 mm measured by M-mode in the long axis. After cannulation of the right femoral vein, a soft-tipped guidewire was advanced through the defect and positioned within a left-sided pulmonary vein. All patients received intravenous heparin (100 IU/kg) during the procedure and intravenous antibiotic prophylaxis as per the center’s standard operating procedures. The size and anatomy of the defect were determined by gentle inflation of a compliant sizing balloon (NMT Medical) across the defect until a waist was apparent. On the basis of this measurement, a BioSTAR implant was selected that was approximately 1.5 to 2 times the balloon-stretched diameter. Delivery and deployment of the device are similar to that previously described for the STARFlex device.3,19–21 Devices available during the study were 23, 28, and 33 mm. After rehydration in heparinized saline, the BioSTAR implant was loaded into a proprietary delivery catheter and advanced to the left atrium via an 11F transeptal sheath. The distal umbrella was opened in the left atrium, and the device and sheath were retracted until the distal umbrella was opposed against the left atrial wall of the septum. The proximal umbrella was then deployed by further withdrawal of the sheath while keeping gentle tension on the device. Correct positioning of the device was confirmed by 2-dimensional and color Doppler TEE imaging in multiple planes, after which the delivery system was activated to release the implant.

Follow-Up
Before discharge, patients underwent transthoracic echocardiography (TTE) to confirm correct device position. All patients continued taking aspirin 75 mg once daily and clopidogrel 75 mg once daily, each for 90 days after the implant procedure. Contrast TTE was performed at baseline (before closure) and at 30 days and 6 months after closure. Residual shunts were assessed by contrast TTE, at rest and during Valsalva maneuver, according to a specified protocol. Shunt size was graded as negative (no bubbles), trivial (few [<10] scattered bubbles seen in the left heart), moderate (obvious shunts with >10 bubbles at any 1 time seen in the left heart), and large (complete opacification [≥20 bubbles] of a section or all of the left heart). The TEE was also repeated at 30 days to assess the healing response and thrombus formation. Echocardiograms were recorded onto videotape and were subsequently reviewed by an independent core laboratory not involved with the closure procedures (Goettingen, Germany). At each visit, blood was taken for measurement of hematologic and biochemical parameters, C-reactive protein, and erythrocyte sedimentation rate.

A Data, Safety, and Adverse Events Monitoring Committee reviewed and evaluated all reported adverse events. This committee comprised an immunologist, 2 cardiologists, a medical ethicist, and a statistician who were all independent of the study and the sponsor.

The primary end point for the study was defect closure at 6 months, defined as procedural success with no shunt or trivial shunt on TTE. Patients who did not receive a BioSTAR implant or for whom follow-up was not available were excluded from the analysis of the primary end point. The number and percentage of subjects with closure at 6 months are reported. Secondary end points were device success, defined as successful delivery and deployment of the BioSTAR at the intended site and removal of the delivery system, and procedural success, defined as device success and completion of the procedure without the occurrence of major adverse events, including death, major bleeding, thromboembolism, loss of device closure.
placement or structural integrity, and the need for cardiac surgery. Secondary end-point analysis was performed on all patients for whom treatment was attempted. Safety analysis was performed on all patients treated in the study. Prespecified safety end points were death due to any cause, clinically relevant immune reaction to the device, clinically relevant serum C-reactive protein and erythrocyte sedimentation rate levels, clinically relevant device related thrombus, systemic thromboembolism, major bleeding, and need for cardiac surgery to explant the device.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Sixty-eight patients were screened for inclusion in the study between July 2005 and November 2005. Enrollment was evenly distributed among the 6 study sites in the United Kingdom. Details of patient flow through the trial and follow-up are given in Table 1. Patient demographics and indications for treatment are outlined in Table 2.

Fifty-nine BioSTAR implants were attempted in 58 patients (Table 2). All devices were successfully delivered and deployed (100%) with no procedural complications related to the device or delivery system. Overall device success was 97% (57/59), and procedural success was 98% (57/58). In 1 patient with a hemodynamically significant ASD, a 33-mm BioSTAR was initially deployed. On TEE interrogation and before detachment from the delivery system, a single arm of the distal umbrella appeared to have prolapsed into the right atrium. This device was successfully retrieved, and because no larger BioSTAR was available, the defect was closed with an alternative nonstudy device. In a second patient with a PFO and an unusually thick secundum septum, a 28-mm device was initially deployed. On TEE interrogation, this device also appeared to be inadequately positioned and was therefore retrieved and successfully replaced with a 33-mm device. The remaining 56 patients had successful deployment of a single BioSTAR device with low profile and excellent conformability to the anatomy noted on TEE (Figure 2).

Of the 57 patients who had closure with BioSTAR, 1 patient was lost to follow-up, and 56 patients completed the study. Closure of the defect was achieved in 48 (92%) of 52 patients at 30 days and 54 (96%) of 56 patients at 6 months. Six patients did not have contrast studies performed at 30 days because this was introduced as a modification to the original protocol. In 1 of the 2 patients with a significant residual shunt at 6 months, a continuous stream of contrast

### TABLE 1. Patient Recruitment and Outcome

<table>
<thead>
<tr>
<th>Description</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total screened</td>
<td>68</td>
</tr>
<tr>
<td>Screen failures*</td>
<td>7</td>
</tr>
<tr>
<td>No shunt on contrast echocardiography</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
</tr>
<tr>
<td>ASD &gt;13 mm</td>
<td>1</td>
</tr>
<tr>
<td>Safety population†</td>
<td>61</td>
</tr>
<tr>
<td>PFO not crossed</td>
<td>3</td>
</tr>
<tr>
<td>Implant attempted</td>
<td>58</td>
</tr>
<tr>
<td>ASD too large for device</td>
<td>1</td>
</tr>
<tr>
<td>Successful implant</td>
<td>57</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
</tr>
<tr>
<td>Completed study</td>
<td>56</td>
</tr>
</tbody>
</table>

*Withdrawed before catheterization laboratory.
†All patients taken to catheterization laboratory for attempt at BioSTAR implant.

### TABLE 2. Patient Demographics for Treatment Group (n=58)

<table>
<thead>
<tr>
<th>Description</th>
<th>Age, y</th>
<th>Male</th>
<th>Female</th>
<th>Defect type</th>
<th>Defect size mean±SD, mm</th>
<th>Indication for closure</th>
<th>Device size, mm</th>
<th>Procedure</th>
<th>Fluoroscopy time, min</th>
<th>Radiation dose, cGy/m²</th>
<th>TIA indicates transient ischemic attack. Data are presented as mean±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46±8</td>
<td>23 (40)</td>
<td>35 (60)</td>
<td>PFO</td>
<td>54 (93)</td>
<td>Hemodynamic</td>
<td>23</td>
<td>41±16</td>
<td>7.3±6.3</td>
<td>1627±1998</td>
<td>Cryptogenic stroke/TIA 50 (86.2) Decompression illness 4 (6.9) Orthodeoxia platypnea 0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>19* (32)</td>
<td>5 (9)</td>
<td>ASD</td>
<td>4 (7)</td>
<td></td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One patient had a 28-mm device that was withdrawn and replaced with a 33-mm BioSTAR.

![Figure 2. TEE image of BioSTAR immediately after implantation (arrow) demonstrating excellent conformability of the device to the native tissue and its exceptionally low profile in vivo. LA indicates left atrium; RA, right atrium; and Ao, aorta.](image-url)
was noted in the left heart that was suggestive of an additional pulmonary shunt.

Sixty-one patients were in the safety population, including all patients in whom a BioSTAR implant was attempted and 3 in whom no PFO was crossed and no implant performed. There were no major adverse events at implant or during follow-up; no devices required explantation, and no major safety issues with BioSTAR were identified.

Five patients required treatment for transient atrial arrhythmia after implantation (1 cardioversion and 4 medical treatment). These patients tended to be older, with an average age of 50 years, and 3 had an atrial septal aneurysm, both of which are factors known to predispose to arrhythmia.10,24

The 30-day postimplant TEE was performed in 54 (96%) of 56 patients. In all patients, the device was noted to be well positioned, with a low profile on the atrial septum. In 1 patient, a mobile echogenic mass was noted on the right atrial side of the device. This was initially interpreted as part of the collagen matrix; as a precaution, however, the patient received anticoagulation therapy, and on repeat TEE, on completion of the study, the mass had fully resolved.

The results of analyses of markers are given in Table 3. There was no evidence of a systemic adverse response in any patient. One patient developed urticaria after device implant, with no increase in C-reactive protein or erythrocyte sedimentation rate levels. The symptoms resolved spontaneously.

**Discussion**

In the present study, we have demonstrated for the first time in humans the feasibility, safety, and efficacy of a novel bioabsorbable implant for the treatment of ASD and PFO. The BioSTAR septal repair implant used in the present study demonstrated closure rates superior to those reported previously with conventional synthetic devices4,5,7 and is the first bioabsorbable device for the treatment of structural heart defects in humans.

Atrial septal repair is the most common cardiac intervention for structural heart disease, with procedures predominately being performed at a young age. Currently available devices are composed mainly of metallic wires with synthetic fabrics. After a variable period of time, these devices become encapsulated by fibrous tissue, which effectively seals the defect, thereafter rendering the implant redundant. In humans, histopathological assessment of explanted devices several years after implantation has shown persistence of a local inflammatory response characterized by lymphocytic tissue infiltration and multinucleated foreign-body giant cells,18 and the potential for late unexpected complications thus remains.

The well-described occurrence of late erosion in some devices is of particular concern.12–14 Furthermore, because of their permanent nature, these implants will obstruct transseptal access to the left atrium should it be required in the future for the treatment of acquired heart disease. Technologies now evolving for the treatment of left-sided heart disease include percutaneous heart valve repair and replacement, left atrial appendage closure, and arrhythmia intervention, with further interventions likely to emerge over the course of current patients’ lives.25 A septal repair implant that is absorbed and remodels into the patient’s own tissue is appealing because little or no foreign material remains, thereby minimizing the potential for late complications and preserving access to the left atrium.

A key advantage of the highly purified, acellular type I collagen matrix used in BioSTAR over synthetic scaffold materials is its unique ability to induce a host connective tissue response that results in site-specific tissue regeneration as opposed to scar tissue formation.26–29 It is derived from porcine intestinal collagen and is only mildly immunoreactive because of its phylogenetically well-conserved primary sequence and helical structure.80 In addition, the proprietary cleaning mechanism applied to the ICL used in BioSTAR devices removes cells, cellular debris, and other noncollagenous components (DNA, RNA, lipids, and glycosaminoglycans) that may also cause an inflammatory response. The process is detergent- and enzyme-free, thus preserving the structural integrity, cell compatibility, and mechanical strength of the matrix and its ability to remodel.30,31 The material is also unique in that cross-linking with carbodiimide can specifically alter the mechanical and biological characteristics of the material. Increasing the degree of cross-linking increases biodegradation time by making the collagen less susceptible to enzymatic degradation, reduces the antigenicity, increases the tensile strength, and decreases the physical softness of the scaffold.31,32 Moreover, the ICL matrix can incorporate bioactive substances. The BioSTAR device makes use of this property in that it has a heparin-coated surface. Preclinical experiments have demonstrated more rapid and complete endothelialization of this matrix than with non–heparin-coated devices, with a low immune response during gradual absorption and replacement by host tissue.22,23

In the present study, we report the first clinical use of the BioSTAR device in patients with a clinically significant atrial-level shunt. Our results demonstrate a high rate of shunt closure at both 30 days and 6 months. Residual shunts were assessed by contrast TTE after a specified protocol of provocative maneuvers. The high early closure rate may be due in part to the impermeable nature of the collagen matrix. In addition, biological interaction between the ICL and host

**TABLE 3. Immunologic Markers**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>12 Weeks</th>
<th>26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP, mg/L</td>
<td>1.3 (0.1–11.2)</td>
<td>2.5 (0.3–32.2)</td>
<td>1.2 (0.2–136.4)</td>
<td>1.3 (0.2–13.9)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>53</td>
<td>48</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>5 (2–12)</td>
<td>5 (2–31)</td>
<td>5 (2–48)</td>
<td>5 (2–26)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>43</td>
<td>37</td>
<td>42</td>
</tr>
</tbody>
</table>

hsCRP indicates high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate.

*One patient demonstrated a transient increase in CRP associated with an intercurrent infection.
tissue, augmented by what we believe to be an intermolecular attraction, incorporates the device into the atrial septum at an early stage, which results in an effective and complete edge-to-edge seal. This process was evident from the exceptional low profile and conformability of the device noted on TEE immediately after implantation and at 30 days (Figure 2).

In the present study, no attempt was made to select patients with more favorable anatomy, and no patient with a PFO was excluded on the basis of defect size or presence of an aneurysm. Additionally, no modification of the septal anatomy was performed (ie, septal puncture or balloon pull-through). The high closure rate demonstrated by BioSTAR confirms its effectiveness in treating the majority of anatomic variants.

There were no major adverse events during the study, and no major safety issues related to BioSTAR were identified. The porcine ICL used in this implant is acellular and RNA-, DNA-, and pyrogen-free. This and similar materials have been successfully used in tissue repair elsewhere in the body. We found no evidence of a systematic inflammatory response to the collagen. One patient developed urticaria after implant that resolved spontaneously. Inflammatory markers were not raised in this patient, and on specialist review and adjudication by the Data, Safety, and Adverse Events Monitoring Committee, this was considered most likely a medication reaction. No other clinically relevant responses were observed.

The Rapid Transport delivery system and the MP35N framework are identical to those used on STARFlex, which has a proven safety record. The framework holds the ICL in place with little risk of erosion, as is reported with woven-wire–configured devices. The BioSTAR implant is easily deployed and, if required, retrievable before release, as was demonstrated in 2 patients in the present study.

Atrial arrhythmia is a common complication after placement of all transeptal devices. Symptoms normally develop within the first 2 weeks after implantation and usually resolve within 1 to 2 months. In the present study, atrial arrhythmia that required treatment occurred in 5 patients. This rate is consistent with previous studies. On completion of the study, all symptoms had resolved in these patients, and only 1 was still taking antiarrhythmic medication. The patients who developed arrhythmia in the present study had a heparin coating. In preclinical experiments, this has been shown to significantly reduce protein and blood cell deposition and to enhance healing.

Thromboembolic events are a recognized complication of all currently used devices. The BioSTAR implants used in the present study had a heparin coating. In preclinical experiments, this has been shown to significantly reduce protein and blood cell deposition and to enhance healing. Although 1 patient in the present study had an echogenic mass noted on the right atrial side of the device on TEE at 30 days, the precise nature of this mass was not clear. As a precaution, the patient was given anticoagulation therapy, and on completion of the study, the mass was noted to have resolved with no clinical consequences.

Conclusions

BioSTAR is a novel septal repair implant designed to provide biological closure of atrial-level defects using the patient’s natural healing response. In the present study, we have demonstrated the safety, feasibility, and effectiveness of BioSTAR for the closure of ASD and PFO in humans with a high rate of early and complete shunt closure. Because 90% to 95% of the implant is absorbed and replaced with host tissue, future access to the left atrium may be achieved. Studies to evaluate long-term safety and effectiveness and to compare BioSTAR with other approved devices are now warranted.

Acknowledgments

The authors would like to thank Dr Dietmar Bartmus (University of Goettingen, Germany) for his dedication and thorough echocardiography review. We would also like to thank members of the Data, Safety, and Adverse Events Monitoring Committee for their commitment and review of the study.

Sources of Funding

This trial was supported by a grant provided by NMT Medical (Boston, Mass).

Disclosures

Dr R Mullen, Hildick-Smith, De Giovanni, Duke, and Jux have received payment for teaching at NMT Medical. Drs Mullen and Hildick-Smith have an ownership interest in NMT Medical. The other authors report no conflicts.

References


Disclosures

Drs Mullen, Hildick-Smith, De Giovanni, Duke, and Jux have received payment for teaching at NMT Medical. Drs Mullen and Hildick-Smith have an ownership interest in NMT Medical. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

The present study is the first human study to evaluate the feasibility of bioabsorbable materials inside the heart. It will likely open research into other biomaterials and other applications as the number of structural heart disease indications increases.

Of particular interest, this material remodels into native tissue. All current mechanical closure technologies may obstruct the atrial septum for life. Many technologies are currently in use or in development that require unfettered access to the left atrium via the right. Technologies that restore a normal septum may be of significant patient benefit by avoiding median sternotomies to correct acquired cardiac disease. From a more practical perspective, the results of this study indicate that the BioSTAR septal repair implant provides very rapid and complete closure of atrial-level defects in an unselected population with patent foramen ovale. This may yield significant benefits for patients in that the device can achieve closure in 30 days, whereas it can take other devices up to 1 year to accomplish closure. The nonporous nature of the material and its properties result in a device that “adheres” securely to the septum.
BioSTAR Evaluation STudy (BEST): A Prospective, Multicenter, Phase I Clinical Trial to Evaluate the Feasibility, Efficacy, and Safety of the BioSTAR Bioabsorbable Septal Repair Implant for the Closure of Atrial-Level Shunts
Michael J. Mullen, David Hildick-Smith, Joseph V. De Giovanni, Christopher Duke, W. Stewart Hillis, W. Lindsay Morrison and Christian Jux

_Circulation_. 2006;114:1962-1967; originally published online October 24, 2006; doi: 10.1161/CIRCULATIONAHA.106.664672

_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/114/18/1962

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/