Balloon Atrial Septostomy Is Associated With Preoperative Stroke in Neonates With Transposition of the Great Arteries

Patrick S. McQuillen, MD; Shannon E.G. Hamrick, MD; Marta J. Perez, BA; A. James Barkovich, MD; David V. Glidden, PhD; Tom R. Karl, MD; David Teitel, MD; Steven P. Miller, MD

Background—Preoperative brain injury is common in neonates with transposition of the great arteries (TGA). The objective of this study is to determine risk factors for preoperative brain injury in neonates with TGA.

Methods and Results—Twenty-nine term neonates with TGA were studied with MRI before cardiac surgery in a prospective cohort study. Twelve patients (41%) had brain injury on preoperative MRI, and all injuries were focal or multifocal. None of the patients had birth asphyxia. Nineteen patients (66%) required preoperative balloon atrial septostomy (BAS). All patients with brain injury had BAS (12 of 19; risk difference, 63%; 95% confidence interval, 41 to 85; P=0.001). As expected on the basis of the need for BAS, these neonates had lower systemic arterial hemoglobin saturation (SaO2) (P=0.05). The risk of injury was not modified by the cannulation site for septostomy (umbilical versus femoral, P=0.8) or by the presence of a central venous catheter (P=0.4).

Conclusions—BAS is a major identifiable risk factor for preoperative focal brain injury in neonates with TGA. Imaging characteristics of identified brain injuries were consistent with embolism; however, the mechanism is more complex than that of vascular access for BAS or exposure to central venous catheters. These findings have implications for the indications for BAS, timing of surgical repair, and use of anticoagulation in TGA. (Circulation. 2006;113:280-285.)

Key Words: balloon ■ heart defects, congenital ■ magnetic resonance imaging ■ stroke ■ transposition of great vessels

Preoperative brain injury is increasingly recognized as a major contributor to the significant burden of neurodevelopmental impairment in neonates with congenital heart disease.1–3 In an initial prospective cohort study with advanced MRI to determine the timing and mechanism of brain injury in neonates with d-transposition of the great arteries (TGA), we observed a 40% incidence of preoperative brain injury, with only 1 new lesion (10%) detected on the postoperative study.4

Many studies of neurodevelopmental outcome in congenital heart disease have focused on neonates with TGA because this group is relatively homogeneous in cardiac anatomy with few associated genetic syndromes and a favorable reparative strategy.5–12 These characteristics of TGA allow investigators to isolate the contribution of perioperative events that influence neurodevelopmental outcome. The Boston Circulatory Arrest Trial demonstrated that use of low-flow cardiopulmonary bypass rather than circulatory arrest during arterial switch decreased the incidence of postoperative seizures5 and resulted in higher neurodevelopment scores at 1 year.6 However, differences between groups disappeared by 4 years of age,7 a finding confirmed at school age.11 Moreover, the cohort as a whole performed below population norms for many end points. Although repair of TGA with full-flow cardiopulmonary bypass may further improve mean full-scale IQ scores, patients still perform worse than unoperated best-friend control subjects.13 These residual impairments, together with observations of preoperative and postoperative injury, underscore the importance of elucidating nonoperative mechanisms that contribute to brain injury.

After birth, viable neonates with TGA must have mixing of oxygenated and deoxygenated blood at the atrial and/or ductal levels to achieve acceptable oxygen delivery.14 Almost 40 years ago, Rashkind and Miller15 reported the procedure for creation or enlargement of an interatrial septal defect for the palliative treatment of neonates with TGA and inadequate mixing. With isolated exceptions, balloon atrial septostomy (BAS) has been safely and effectively applied. In our initial cohort of 10 neonates with TGA, all patients with preoperative brain injury also underwent BAS.4 The objective of this study was to determine whether BAS is an independent risk factor for acquired preoperative brain injury in a larger cohort of term neonates with TGA.

Methods

Patients

Since September 2001, we have studied 29 consecutive neonates with TGA (born in or transferred to our institution) using preoper-
Neonates were excluded if gestational age at birth was <36 weeks or if there was a suspected or confirmed congenital infection or genetic malformation syndrome. Neonates were studied after voluntary, informed parental consent was obtained. The University of California, San Francisco Committee on Human Research approved the study protocol.

During the study period, the on-service pediatric cardiologist evaluated all neonates with TGA preoperatively to determine the need for a BAS. The indication for BAS was based on systemic arterial oxygen saturation (SaO₂), clinical assessment of cardiac output, and patency/size of the interatrial communication by echocardiography.

### Balloon Atrial Septostomy

BAS was performed at the bedside using echocardiographic guidance in most patients. In a minority of patients, BAS was performed in the catheterization laboratory with fluoroscopic guidance (n=2 of 19). BAS was performed at 3 institutions, including the study site (n=16) and 2 referring institutions before transfer (n=3), using the same indications and similar techniques for the procedure. Vascular access was obtained through either the femoral or umbilical vein with sterile technique. Heparin administration was identified in only 1 patient. A 5F Fogarty catheter was advanced directly through the umbilical vein or through a 7F sheath placed in the femoral vein. With echocardiographic or fluoroscopic guidance, the balloon-tipped catheter was placed across the atrial septum, inflated, and withdrawn into the right atrium. The procedure was repeated until adequate atrial communication was achieved. It was considered successful in all patients, and no complications from the procedure were noted.

### Data Collection

Perioperative data were prospectively collected from the medical records by a team of neonatal research nurses and reviewed by a pediatric intensivist who was blinded to the neuroimaging findings. A validated composite score of physiological and laboratory data was used to measure overall illness severity (Score for Neonatal Acute Physiology–Perinatal Extension [SNAP-PE]) within 24 hours of admission.16 A resuscitation score was assigned on the basis of intervention administered at birth ranging from 1 (no intervention) to 6 (endotracheal intubation, atropine or epinephrine with or without chest compressions).17

### MRI Studies

The preoperative MR studies were performed as soon as the baby was stable enough to be transported safely to and from the MR scanner with a specialized MRI-compatible isolette that included an additional neonatal head coil.18 A team of intensive care nurses accompanied the patient. An intensive care physician in the MR suite monitored the neonates during scanning and ventilated the intubated neonates by hand. If necessary, pharmacological sedation with pentobarbital (1- to 2-mg/kg dose up to a total of 6 mg/kg) and/or morphine sulfate (0.05-mg/kg dose up to a total of 0.2 mg/kg) was administered by the monitoring physician according to the sedation guidelines at our institution. In this cohort, no adverse events occurred with this scanning protocol.

All studies were done on a 1.5-T Signa Echo-Speed system (GE Medical Systems): (1) T1-weighted sagittal spin echo images (4-mm thickness) using a repetition time (TR) of 500 ms, echo time (TE) of 11 ms, 1 excitation, and 192x256 acquisition matrix; (2) dual-echo T2-weighted spin echo (4-mm thickness) with a TR of 3000 ms, TE of 60 and 120 ms, and 192x256 acquisition matrix; and (3) coronal volumetric 3-dimensional gradient echo images with radiofrequency spoiling, spoiled gradient recalled images (1.5-mm thickness) with a TR of 36 ms, a TE of 9 ms, a flip angle of 35°, and 1 excitation. Diffusion tensor imaging was acquired in 4.8 minutes with a multirepetition, single-shot echo-planar sequence with 6 gradient directions, b=0 and 700 s/mm², TR of 7 seconds, TE of 99.5 ms, 3 repetitions, field of view of 36x18 cm, matrix of 256x128, slice thickness of 3 mm with no gap, 162xKHz readout bandwidth, and no rbf sampling, with a resulting in-plane resolution of 1.4 mm. The diffusion imaging data were postprocessed to generate maps of average diffusivity ($D_v$).19

A neuroradiologist reviewed the MRI scans for acquired focal, multifocal, or global changes. Beyond corrected gestational age and cardiac anatomical diagnosis, the neuroradiologist was unaware of all other patient clinical information, including Apgar score, preoperative neurological examination, and need for invasive instrumentation, including BAS. Acquired focal and multifocal lesions included infarction, germinal matrix and intraventricular hemorrhage, and white matter injury.20 Focal infarct referred to discrete areas of reduced intensity on $D_v$ maps or focal hyperintensity on T2-weighted images and was described by the extent of the vascular territory involved. Intraventricular hemorrhage was graded according to the system of Papile et al.20 White matter injury included foci of abnormal T1 hyperintensity in the absence of marked T2 hypointensity in the white matter and foci of low intensity on T1-weighted images, with or without corresponding areas of reduced intensity on $D_v$ maps. White matter injury was scored as normal, minimal, moderate, or severe with a system applied successfully in our studies of premature neonates: Normal (no white matter lesions), minimal (≤3 areas of T1 signal abnormality measuring <2 mm), moderate (>3 areas of T1 signal abnormality or these areas measured >2 mm but <5% of the hemisphere involved), or severe (>5% of the hemisphere involved).21 Given the potential overlap in anatomic distribution and origin of these acquired focal/multifocal injuries, we characterized infarction, intraventricular hemorrhage, and white matter injury as acquired injury. The presence of subdural hemorrhage commonly seen after delivery22 was noted separately.

### Data Analysis

Clinical variables in neonates with and without preoperative brain injury were compared with Stata version 8 (Stata Corp) using the Mann Whitney U test for continuous or ordinal data and Fisher's exact test for categorical variables.

### Results

#### Preoperative MRI

Twelve neonates with TGA (41%) had acquired focal brain injury on the preoperative MRI scan (Figure). Newborns with and without acquired brain injury did not differ with respect to gestational age at birth or age at MRI examination. Importantly, although many patients had very low SaO₂, no patient had changes in a basal ganglia or watershed pattern of injury consistent with global hypoxic ischemic brain injury in the term newborn.23 Acquired injuries observed included focal infarct in 5 neonates (Figure, A), focal white matter injury in 2 (Figure, B), intraventricular hemorrhage in 1, and a combination of lesions in 4: Focal infarct and white matter injury in 3 and focal infarct and intraventricular hemorrhage in 1. Focal injury involved the middle cerebral artery territory in 7 patients and the posterior cerebral artery in 3. Focal infarcts were small (less than one third of the arterial territory) in 8 neonates and moderately sized (one third to two thirds of the arterial territory) in 1 patient. The severity of white matter injury was minimal in 2 neonates, moderate in 1, and severe in 2. Intraventricular hemorrhage involved the subependymal region alone in 1 newborn with extension into the ventricle in another newborn. Three neonates had small subdural hemorrhages without mass effect that were supratentorial in 2 and infratentorial in 1. Only 1 newborn had a developmental venous anomaly, but no developmental malformations of the brain parenchyma were detected.
Clinical Risk Factors for Preoperative Brain Injury

Clinical data, including patient demographics, illness severity, invasive procedures, clinical examination, laboratory data, and preoperative clinical course, were analyzed for association with preoperative brain injury. BAS, 5-minute Apgar, and lowest SaO₂ were significantly associated with brain injury (Table 1).

Although the 5-minute Apgar was significantly lower in infants with preoperative injury, the median value was only lower by 1 point, none of the neonates were depressed at birth, and no patient had a 5-minute Apgar score <6, indicating that no patient suffered significant birth asphyxia based on consensus definition. We also examined the resuscitation score, cord blood gases, and a comprehensive neonatal illness severity score (SNAP-PE) for differences between groups. Infants with preoperative injury did not require more resuscitation at birth, and cord blood gases were similar (Table 1). The SNAP-PE, a validated neonatal illness severity score that incorporates 9 clinical and 22 laboratory variables, was not different between the groups (Table 1).

No patient had an episode of cardiac arrest.

All infants were treated at the time of diagnosis with prostaglandin E₁ (PGE₁). By the time of MRI, however, half of the cohort had been weaned off PGE₁. There were no differences in ongoing treatment with PGE₁ among patients with preoperative injury compared with no injury (Table 1) or patients needing BAS compared with those not needing this procedure (P=0.5).

BAS and Preoperative Brain Injury

Acquired preoperative brain injury was strongly associated with having a BAS. Twelve of 19 infants receiving BAS had injury on MRI. None of 10 neonates with TGA not requiring BAS were injured (risk difference, 63%; 95% confidence interval, 41 to 85; P=0.001). The risk difference for preoperative brain injury corresponds to a number needed to harm of 1.6 neonates (95% confidence interval, 1.2 to 2.4). The single patient who received heparin for BAS also had injury detected on preoperative MRI. However, the fact that this was an isolated observation precludes statistical comparison.

Mechanism of Injury

To determine whether the BAS technique affected the risk of injury, we analyzed the site of vascular access for BAS and...
found that similar cannulation sites had been used for neonates with and without injury (Table 2). Because all identified brain injuries appeared focal and thus consistent with embolism, we examined the presence, duration, and timing of removal of any central venous catheters for association with brain injury. Brain injury was not significantly associated with the presence of an umbilical venous or arterial catheter at any time preoperatively (Table 1). The duration of umbilical venous or arterial catheterization before the MRI study also was not associated with acquired brain injury (Table 1). Injured infants underwent BAS earlier than uninjured infants (median day of life, 1 [range, 1 to 2] versus 2 [range, 1 to 6]; \( P = 0.04 \)).

### Discussion

BAS is a significant risk factor for acquired preoperative brain injury in neonates with TGA. In fact, only neonates exposed to BAS had preoperative brain injury. The incidence of brain injury in BAS-exposed patients was 61%, indicating that 1.6 BAS procedures need to be performed to result in a patient with brain injury. None of these injuries had been suspected clinically, and other clinical risk factors were not identified. The lesions that we identified are of concern, because white matter injury and stroke are linked to adverse neurodevelopmental outcome in infants with neonatal encephalopathy.20,23 This cohort is being followed up to specifically determine the significance of these lesions in infants with TGA.

A significant but inevitable limitation of this study is the potential for confounding by the fact that neonates with TGA and a restrictive atrial septum who require a BAS by definition have more hypoxemia and, in certain instances, hemodynamic instability. Lower saturations in this group account in part for the lower 5-minute Apgar scores, because cyanosis is 1 of 5 variables in the Apgar score. Only 1 infant had an abnormal 5-minute Apgar score (<7), and no infant suffered birth asphyxia based on consensus definition.24 More importantly, indexes of symptomatic birth asphyxia did not differ between injured and uninjured patients. Specifically, cord blood gases, resuscitation scores, and illness severity scores were not different between groups. Nonetheless, our group was not randomized, and the sample size precludes multivariable analysis and limits the power to detect differences between groups. In comparison, in a study of 124 term neonates with encephalopathy and abnormal perinatal depression, only 6 patients developed focal stroke, indicating that illness severity and stroke are not necessarily tightly linked.25 Finally, birth asphyxia or cyanosis in a neonate with TGA would be expected to result in global hypoxia or ischemia. Impaired global oxygen-substrate delivery results in characteristic patterns of injury, including injury to the deep gray nuclei or cortical injury in a parasagittal watershed distribution.20,23 These characteristic patterns were not observed. Despite the magnitude of the association between BAS and preoperative brain injury, to prove that BAS caused the injuries we observed would require a preprocedural MRI. However, the indications for BAS preclude safely obtaining an MRI in these patients. In a parallel study, we are attempting to address this issue by prenatal diagnosis and fetal MRI.

All injuries identified after BAS in both gray and white matter locations were focal or multifocal and consistent with

### TABLE 1. Clinical Characteristics of Neonates With and Without Acquired Preoperative Brain Injury

<table>
<thead>
<tr>
<th></th>
<th>No Brain Injury (n=17)</th>
<th>Acquired Brain Injury (n=12)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (82)</td>
<td>10 (83)</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3525 (2640 to 4745)</td>
<td>3250 (2451 to 4680)</td>
<td>0.08</td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>34 (32 to 38)</td>
<td>34 (32 to 37)</td>
<td>0.5</td>
</tr>
<tr>
<td>1-min APGAR</td>
<td>8 (3 to 9)</td>
<td>7 (1 to 8)</td>
<td>0.4</td>
</tr>
<tr>
<td>5-min APGAR</td>
<td>9 (6 to 9)</td>
<td>8 (6 to 9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Resuscitation score</td>
<td>2 (1 to 4)</td>
<td>2 (1 to 5)</td>
<td>0.1</td>
</tr>
<tr>
<td>SNAP-PE</td>
<td>14 (9 to 26)</td>
<td>19.5 (9 to 30)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lowest ( \text{SaO}_2 ) saturation recorded</td>
<td>70 (26 to 82)</td>
<td>50 (20 to 70)</td>
<td>0.05</td>
</tr>
<tr>
<td>Lowest base deficit</td>
<td>(-8 (-19 to 7))</td>
<td>(-4 (-28 to 0.4))</td>
<td>0.2</td>
</tr>
<tr>
<td>BAS, n (%)</td>
<td>7 (41)</td>
<td>12 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>PGE1 at day of MRI, n (%)</td>
<td>7 (41)</td>
<td>8 (67)</td>
<td>0.3</td>
</tr>
<tr>
<td>Umbilical artery catheter, n (%)</td>
<td>13 (76)</td>
<td>11 (91)</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of catheterization before MRI, d</td>
<td>3 (0 to 9)</td>
<td>3 (0 to 5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Umbilical vein catheter, n (%)</td>
<td>11 (65)</td>
<td>10 (83)</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration of catheterization before MRI, d</td>
<td>1 (0 to 9)</td>
<td>3 (0 to 6)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are median (range) when appropriate.

### TABLE 2. Cannulation Site for BAS in Neonates With and Without Preoperative Brain Injury

<table>
<thead>
<tr>
<th></th>
<th>No Brain Injury, n (%)</th>
<th>Acquired Brain Injury, n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical</td>
<td>2 (29)</td>
<td>2 (17)</td>
<td>0.8</td>
</tr>
<tr>
<td>Femoral</td>
<td>4 (57)</td>
<td>8 (67)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1 (14)</td>
<td>2 (17)</td>
<td></td>
</tr>
</tbody>
</table>
emboli. BAS is associated with multiple risk factors for thrombosis related to both vascular access and the effects of the procedure itself. We did not identify a difference in the risk of brain injury by route of vascular access (umbilical versus femoral). The reason may be the competing risks of either route. Cerebral infarction after BAS by the umbilical route has been reported and may have been due to displacement of preexisting thrombus, possibly from the ductus venosus, as imaged during the procedure.26 The incidence of femoral or iliac vein thrombosis after catheterization by the femoral venous route is significant, with the highest incidence occurring in neonates with TGA requiring BAS (59%).27 Infants with injury underwent BAS significantly earlier than uninjured infants, suggesting that urgency of the procedure may increase the risk of injury through either patient-related (eg, illness severity) or procedural (eg, emergent) risk factors.

In neonates with TGA and intact ventricular septum, the size of the foramen ovale is the primary factor influencing mixing and thus SaO2.28 BAS is intended to produce a tear in the atrial septum primum,29 a structure that may vary in thickness.30 The tears are associated with acute pathology that includes hemorrhage within the subendocardium and fibrin tags at the margins of the defect.31 Although thromboembolism or embolized atrial septum has not been observed in animal models of this procedure, clearly thrombi at the site of vascular access and in situ at the tear in the atrial septum are possible sources of brain emboli. Catheter-associated thromboemboli are unlikely to explain these observations, because we did not observe a single stroke in subjects not exposed to BAS, despite a similar prevalence of central venous catheters. There is likely a multifactorial component to brain injury in neonates with TGA. In these neonates, brain lactate is elevated on preoperative MR spectroscopy, indicating increased cerebral metabolism.3,4 Cyanosis itself over a prolonged time frame is associated with impaired cognitive function.32 These factors may lead to injury susceptibility to postnatal stressors such as embolic injury.

Patients with TGA have a generally favorable neurodevelopmental outcome compared with those with other forms of congenital heart disease, and mean IQ at school age is in the normal range.11,12 However, these children still have significant impairments of motor function12 and visual-spatial skills.11 Learning disability, behavioral disorders and hyperactivity are noted with a high prevalence.33 Clearly, there is residual burden of injury that may be preventable. The relationship of BAS to neurodevelopmental outcome has not been reported in any of the large studies of this issue.5–9,11,12,33 Although, emergency BAS was identified as a risk factor in a smaller study,34 this association did not reach significance. Furthermore, these patients represented less than one quarter of all patients exposed to BAS; they also had severe hypoxemia and acidosis. Identification of preoperative stroke presented an issue for the management of patients with regards to timing of surgery and incumbent exposure to anticoagulation and cardiopulmonary bypass. Our practice was to obtain a pediatric neurology consultation to assist with immediate clinical management and for long-term follow-up. In a minority of patients (n=4 of 12) with multiple lesions or a single large lesion, surgery was delayed 7 to 14 days. In no case did preoperative lesions enlarge or undergo hemorrhagic transformation after surgery. BAS is strongly associated with preoperative stroke in neonates with TGA. These strokes were not clinically apparent, which likely explains why this observation has been heretofore unrecognized. Despite optimizing intraoperative care, there remains significant burden of neurodevelopmental impairment in this population. The findings of this study indicate that clinical trials are needed to evaluate modifications to the procedure or attempts to avoid BAS with early surgical intervention, because these strategies may be associated with independent risks such as bleeding or prolonged hypoxia.

Acknowledgments

This work was supported by an American Heart Association Beginning Grant-in-Aid (0365018Y), the Larry L. Hillblom Foundation (start-up grant 2002/3E), and a gift from D.N. & E. Walter & Co. This study was carried out in part in the Pediatric Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by the National Center for Research Resources (5 M01 RR-01271), US Public Health Service. We thank the study nurses of the University of California, San Francisco Pediatric Clinical Research Center and Drs Jeffrey Fineman and Ian Adatia for critical reading of the manuscript.

Disclosures

None.

References

9. Ellerbeck KA, Smith ML, Holden EW, McMenamin SC, Badawi MA, Brenner JJ, Kan JS, Hyman SL. Neurodevelopmental outcomes in...
McQuillen et al  Balloon Septostomy Is a Risk Factor for Stroke  285


CLINICAL PERSPECTIVE

Preoperative MRI identified a startling 61% incidence of stroke after BAS in neonates with TGA. No patient unexposed to BAS was found to have preoperative stroke. BAS, or the Rashkind procedure, has been used for 40 years to improve hemoglobin saturation and palliate neonates with TGA before surgery. By stabilizing patients and allowing for recuperation before surgery, BAS has contributed to the development of definitive surgical techniques for repair of TGA. Although advances in the care of neonates with TGA have resulted in generally favorable neurodevelopmental outcomes, these infants continue to perform below population norms for many end points. The present observations suggest a mechanism for this residual impairment that may be preventable. Although similar strokes are associated with adverse neurodevelopmental outcome in other groups of term neonates, the exact significance of these injuries for infants with TGA remains to be determined by follow-up of this cohort. The safety profile and clear benefits of BAS have resulted in widespread use of this procedure. Clinicians caring for newborns with TGA should be cognizant of the high risk of strokes and factor this risk into the decision to perform BAS.
Balloon Atrial Septostomy Is Associated With Preoperative Stroke in Neonates With Transposition of the Great Arteries
Patrick S. McQuillen, Shannon E.G. Hamrick, Marta J. Perez, A. James Barkovich, David V. Glidden, Tom R. Karl, David Teitel and Steven P. Miller

_Circulation_. 2006;113:280-285; originally published online January 9, 2006;
doi: 10.1161/CIRCULATIONAHA.105.566752

_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/113/2/280

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/