Predictors of Outcome in Chronic Thromboembolic Pulmonary Hypertension

Diana Bonderman, MD; Nika Skoro-Sajer, MD; Johannes Jakowitsch, PhD; Christopher Adlbrecht, MD; Daniela Dunkler, MSc; Sharokh Taghavi, MD; Walter Klepetko, MD; Meinhard Kneussl, MD; Irene M. Lang, MD

Background—Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by intraluminal thrombus organization and fibrous obliteration of pulmonary arteries. Recently, associated medical conditions such as splenectomy, ventriculoatrial shunt for the treatment of hydrocephalus, permanent central intravenous lines, inflammatory bowel disease, and osteomyelitis were found to be associated with the development of CTEPH. The study aim was to define the impact of these novel risk factors on survival.

Methods and Results—Between January 1992 and December 2006, 181 patients diagnosed with CTEPH were tracked with the use of our center’s customized computer database. A Cox regression model was used to examine relations between survival and associated medical conditions, age, sex, hemodynamic parameters, modified New York Heart Association functional class at diagnosis, CTEPH type, pulmonary endarterectomy, and anti-cardiolipin antibodies/lupus anticoagulant. During a median observation time of 22.1 (range, 0.03 to 152) months, the clinical end point of cardiovascular death or lung transplantation occurred in 48 cases (27%). Pulmonary endarterectomy (hazard ratio, 0.14; 95% CI, 0.05 to 0.41; \( P = 0.0003 \)), associated medical conditions (hazard ratio, 3.17; 95% CI, 1.70 to 5.92; \( P = 0.0003 \)), and pulmonary vascular resistance (hazard ratio, 1.02; 95% CI, 1.00 to 1.04; \( P = 0.04 \)) were predictors of survival. Thirty-day postoperative mortality (24% versus 9%) and the incidence of postoperative pulmonary hypertension (92% versus 20%) were substantially higher in patients with associated medical conditions.

Conclusions—CTEPH-predisposing medical conditions, such as splenectomy, permanent central intravenous lines, and certain inflammatory disorders, predict poor survival in CTEPH. (Circulation. 2007;115:2153-2158.)

Key Words: hypertension, pulmonary \( \text{I} \) survival \( \text{I} \) thrombosis

Chronic thromboembolic pulmonary hypertension (CTEPH) results from obstruction of the pulmonary vascular bed by nonresolving thromboemboli. CTEPH is thought to account for a large number of pulmonary hypertension diagnoses.\(^1\) It has been estimated that 2500 new cases of CTEPH occur each year in the United States.\(^2\) One subset of CTEPH represents the complication of acute pulmonary embolism, which has been estimated to lead into CTEPH in 3.8% within 2 years.\(^3\)

In contrast to pulmonary arterial hypertension (PAH), which manifests in pulmonary vessels of <300-\(\mu\)m diameter, CTEPH has been initially discriminated from PAH by its major-vessel involvement of the vascular remodeling process,\(^4\) rendering it accessible to surgical intervention with removal of the obstructing lesions.\(^5\) Accordingly, pulmonary endarterectomy (PEA) has been considered the treatment of choice for CTEPH.\(^6\) Untreated patients with CTEPH progress to right heart failure and death,\(^7\) although generally more slowly than patients with PAH.\(^8\) Concomitant small-vessel arteriopathy is present at various degrees in patients with CTEPH.\(^9\) In \( \approx 10\% \) of these patients, pulmonary hypertension does not resolve despite removal of significant amounts of organized thrombus. Persistent pulmonary hypertension after PEA remains a significant problem because of its association with increased morbidity and mortality. More than one third of perioperative deaths and nearly half of long-term deaths have been attributed to persistent pulmonary hypertension.\(^10\)

CTEPH patients are heterogeneous with respect to their hemodynamic status, surgical accessibility of pulmonary thromboemboli, presence and titer of anti-cardiolipin antibodies/lupus anticoagulant,\(^11,12\) and concomitant conditions.\(^13\) Individuals with surgical accessibility of pulmonary thromboemboli may normalize their hemodynamics and exercise capacity after successful PEA.\(^14\) Large surgical series have revealed that the most proximal location of pulmonary arterial obstructions, labeled as CTEPH-type, and preopera-
tive pulmonary vascular resistance (PVR) critically affect surgical mortality.  

Recently, distinct medical conditions (referred to as associated medical conditions) have been linked to the development of CTEPH. These include splenectomy and ventilocuatrial shunt for the treatment of hydrocephalus, as well as chronic central intravenous lines, inflammatory bowel disease, and osteomyelitis.  

On the basis of increasing knowledge of the pathophysiology of CTEPH (summarized recently in an international symposium on CTEPH), the aim of the present study was to define new predictors of outcome in CTEPH.

### Methods

#### Setting

The Vienna PEA Program is located in the Medical University of Vienna, Vienna, Austria. Possible surgical candidacy of every CTEPH patient in Austria is evaluated at this institution.

Since 1992, our center has been performing PEAs with perioperative mortality and success rates that are comparable to those of other internationally established centers.  

Coumadin adjusted to a target international normalized ratio between 2.0 and 3.0, oxygen, and diuretics have been conventional medical treatments.

#### Diagnosis of CTEPH

The diagnosis of CTEPH has been established by chest x-ray, transthoracic and transesophageal echocardiography with Doppler, pulmonary function tests including arterial blood gas analysis at rest and exercise, right heart catheterization, pulmonary angiography, ventilation-perfusion scan of the lungs, and multislice and high-resolution computed tomography scans. A panel of cardiologists, pulmonologists, radiologists, and cardiothoracic surgeons reviewed each case. CTEPH type was classified according to Jamieson et al.  

As follows: type I, presence of a central thrombus; type II, thickened intima, fibrous webs, and bands; type III, occlusions in the segmental and subsegmental branches; or type IV, very distal thrombi. Criteria for PEA have been a resting PVR > 300 dyne·s·cm⁻² (except for patients with unilateral disease) and surgical accessibility of thromboembolic lesions.  

Surgery was withheld if (1) PVR exceeded 1100 dyne·s·cm⁻², (2) surgical PEA criteria were not fulfilled, (3) the patient was suffering from severe comorbidities, or (4) the patient refused PEA.

#### Collection of Clinical Data

Entry into the cohort was defined as the date of first diagnostic right heart catheterization. Subjects were tracked with our center’s computer-based database that was created in January 1992. The database records the date of diagnosis, concomitant diseases, hemodynamic parameters at diagnosis and at follow-up, medical therapy, and date of PEA. In particular, 6 to 12 months after PEA, a routine evaluation of hemodynamics was performed. Thereafter, PEA patients were monitored by annual transthoracic echocardiography. Additional right heart catheterization was performed in all cases with echocardiographic suspicion of pulmonary hypertension.

Deceased subjects and those who underwent lung transplantation were identified by a code. Accurate dates and causes of all deaths were known from the 3- to 6-month ambulatory follow-up. Surviving patients were censored on the date of their last clinic appointment or hospitalization. Death caused by other than cardiac reasons was treated as a censored observation.

#### Statistical Analysis

We calculated the incidence rates for death or lung transplantation and used the Kaplan-Meier method to estimate survival rates. Kaplan-Meier survival curves were compared by the log-rank test. Individual variable analysis based on the proportional hazard model was used to examine the relations between survival and age, sex, cardiac index, mean pulmonary artery pressure, PVR, modified New York Heart Association classification dichotomized in functional classes 1 and 2 versus classes 3 and 4, CTEPH type dichotomized in types 1 and 2 versus types 3 and 4, PEA, anti-cardiolipin antibodies/lupus anticoagulant, and associated medical conditions, ie, prior splenectomy, ventilocuatrial shunt/indwelling intravenous lines, inflammatory bowel disease, and osteomyelitis.  

Multivariable analysis based on the proportional hazard model was used to examine the joint effects of multiple variables on survival, controlling for possible confounders. The number of covariates that could be entered simultaneously was limited by the high degree of collinearity among variables in the same category (eg, hemodynamic parameters). Results are expressed as hazard ratios with 95% CIs. Categorical and continuous variables were compared with the χ² and Fisher exact test and the 2-sample Wilcoxon test, respectively. P<0.05 was considered statistically significant. The study was approved by the Medical University of Vienna Ethics Committee.

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

### Results

#### Patients

A total of 181 patients with CTEPH were registered in the database between January 1992 and December 2006. Baseline characteristics are shown in Table 1. Ninety-four patients were female, and 87 were male. Mean age at diagnosis was 57±16 years. At inclusion, 6 patients were in modified New York Heart Association functional class I, 28 in class II, 77 in...
class III, and 70 in class IV. Sixteen patients (9%) had undergone splenectomy, 7 were ventriculotrial shunt carriers, 3 (6%) had infected pacemaker leads, 9 (5%) had a history of chronic inflammation (inflammatory bowel disease or osteomyelitis), and 23 (13%) carried plasma anticardiolipin antibodies/lupus anticoagulant.

One hundred five patients (58%) underwent PEA. On the basis of the morphology of the surgical specimens and analysis of angiograms and computed tomography scans, thrombus localization within the pulmonary vascular tree was classified as follows: type I, n=24 (23%); type II, n=62 (59%); type III, n=14 (13%); and type IV, n=5 (5%). PEA was not performed because of distal thrombus location in 33 patients, inadequate PVR in 18 patients, and severe comorbidities in 19 patients. Five patients refused PEA. One patient is currently on the waiting list for surgery.

Patients who underwent surgery were significantly younger (52±15 years) than those not undergoing PEA (64±15 years; P<0.0001). Gender distribution was equal between operated (49 men/56 women) and unoperated (38 men/38 women; P=0.65) patients. At 1-year follow-up, hemodynamic parameters in PEA patients had improved significantly compared with non-PEA patients (cardiac index, 3.0±0.6 versus 2.5±0.5 L/min per m²; P=0.04; PVR, 269±201 versus 586.0±248.0 dyne·s·cm⁻³; P=0.003; mean pulmonary artery pressure, 25.4±11.7 versus 45.8±12.7 mm Hg; P<0.001). There was no statistical difference in the number of patients with associated medical conditions undergoing PEA (n=17, corresponding to 49% of all patients with associated medical conditions) and the number of patients with associated medical conditions not treated by PEA (n=18, corresponding to 51% of all patients with associated medical conditions; P=0.21).

Survival

During a median observation time of 22.1 (range, 0.03 to 152) months, 48 end points were reached. Twenty-eight patients died from right heart failure, and perioperative and postoperative in-hospital death occurred in 12 patients. Eight subjects underwent double lung transplantation. Noncardiac death occurred in 12 patients. Forty-three patients (61%) were classified as follows: type I, n=62 (12%); type II, n=18, corresponding to 51% of all patients with associated medical conditions; type III, n=18, corresponding to 51% of all patients with associated medical conditions; type IV, n=18, corresponding to 51% of all patients with associated medical conditions; type I and II with types III and IV. The HRs reflect 25-dyne changes of PVR.

The overall perioperative mortality rate was 11%, with 27% between 1992 and 1995, 15% between 1996 and 1999, and 6% between 2000 and 2004. Since 2004, the perioperative mortality rate has been 5%. Inclusion of patients with associated medical conditions was a negative predictor of survival (hazard ratio, 2.38; 95% CI, 1.02 to 5.56; P=0.045). In the Kaplan-Meier analysis, unoperated patients without associated medical conditions lived significantly longer than unoperated patients with associated medical conditions (P=0.04; Figure, panel B).

Outcomes After PEA

The perioperative mortality rate was 11%, with 27% between 1992 and 1995, 15% between 1996 and 1999, and 6% between 2000 and 2004. Since 2004, the perioperative mortality rate has been 5%. Inclusion of patients with associated medical conditions was a negative predictor of survival (hazard ratio, 2.38; 95% CI, 1.02 to 5.56; P=0.045). In the Kaplan-Meier analysis, unoperated patients without associated medical conditions lived significantly longer than unoperated patients with associated medical conditions (P=0.04; Figure, panel B).

To avoid the therapeutic bias imposed by PEA, we analyzed the subgroup of unoperated patients. Similar to the overall patient cohort, the presence of associated medical conditions was a negative predictor of survival (hazard ratio, 2.38; 95% CI, 1.02 to 5.56; P=0.045). In the Kaplan-Meier analysis, unoperated patients without associated medical conditions lived significantly longer than unoperated patients with associated medical conditions (P=0.04; Figure, panel B).

### Table 2. Individual Variable Cox Proportional Hazard Analysis Relating Survival to Selected Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.98 to 1.02)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex</td>
<td>0.99 (0.56 to 1.75)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.55 (0.29 to 1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>1.00 (0.99 to 1.03)</td>
<td>0.55</td>
</tr>
<tr>
<td>PVR</td>
<td>1.02 (1.00 to 1.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Modified NYHA functional class*</td>
<td>1.38 (0.58 to 3.26)</td>
<td>0.46</td>
</tr>
<tr>
<td>CTEPH type*</td>
<td>0.50 (0.28 to 0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Associated medical conditions</td>
<td>3.58 (2.03 to 6.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACL/LAC</td>
<td>1.06 (0.47 to 2.37)</td>
<td>0.89</td>
</tr>
<tr>
<td>PEA</td>
<td>0.35 (0.19 to 0.64)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; PAP, pulmonary artery pressure.

*Variables were analyzed in a dichotomized manner comparing types I and II with classes/types III and IV. The HRs reflect 25-dyne changes of PVR.

### Table 3. Multivariable Cox Proportional Hazard Analysis Relating Survival to Selected Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index</td>
<td>0.56 (0.28 to 1.13)</td>
<td>0.10</td>
</tr>
<tr>
<td>PVR</td>
<td>1.02 (1.00 to 1.04)</td>
<td>0.04</td>
</tr>
<tr>
<td>CTEPH type*</td>
<td>1.13 (0.50 to 2.55)</td>
<td>0.78</td>
</tr>
<tr>
<td>Associated medical conditions</td>
<td>3.17 (1.70 to 5.92)</td>
<td>0.0003</td>
</tr>
<tr>
<td>PEA</td>
<td>0.14 (0.05 to 0.41)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio.

*Variables were analyzed in a dichotomized manner comparing types I and II with types III and IV. The HRs reflect 25-dyne changes of PVR.
The present study demonstrates that the presence of associated medical conditions predicts increased operative risk and worse long-term outcome in CTEPH. Recently, we have reported that splenectomy,13,16 ventriculoatrial shunt, inflammatory bowel disease, and osteomyelitis13 are risk factors for the development of CTEPH. The present report provides evidence for excessive mortality in CTEPH patients with any of those conditions. Although prognostic factors have been identified clearly in PAH,19 few data exist on prognostic factors specific for CTEPH. In addition, with few exceptions,15,20 no data exist to define preoperative risk in CTEPH patients. Recently, the link between splenectomy and CTEPH has gained considerable attention, with speculation that abnormal postsplenectomy erythrocyte activities or abnormal platelet activation may result in a primarily distal CTEPH subentity.13,16 In fact, CTEPH patients with splenectomy were less likely to undergo PEA (Table 1). However, overall, there was no correlation between CTEPH type and the presence of associated medical conditions and no decreased likelihood of patients with associated medical conditions to undergo PEA. Despite technically successful surgery, patients with associated medical conditions had worse outcomes with higher perioperative mortality (24% versus 9%) and an increased incidence of postoperative pulmonary hypertension (Figure, panel C). On the basis of these data, the role of PEA in patients with associated medical conditions must be redefined. Within the past 4 decades, PEA has been introduced as the treatment of choice for patients with CTEPH.15 The outcomes of PEA with regard to functional status, quality of life, hemodynamics, and right ventricular function have been very favorable. A randomized study comparing PEA with medical treatment has been considered unethical.6 Fedullo and coworkers2 reviewed the world literature on PEA and found perioperative mortality rates between 5% and 24%.

TABLE 4. Comparison of Hemodynamic Parameters Between CTEPH Patients With and Without Associated Medical Conditions Before PEA and 12±7 Months After Successful PEA

<table>
<thead>
<tr>
<th>Variable</th>
<th>+Associated Medical Conditions</th>
<th>−Associated Medical Conditions</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.6±1.3</td>
<td>4.4±1.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.1±0.7</td>
<td>2.3±0.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>50.9±10.7</td>
<td>49.0±13.4</td>
<td>0.52</td>
</tr>
<tr>
<td>PVR, dyne·s·cm⁻⁵</td>
<td>1003±430</td>
<td>831±385</td>
<td>0.09</td>
</tr>
<tr>
<td>After PEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>13</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.8±2.1</td>
<td>5.9±1.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.4±0.8</td>
<td>3.1±0.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>41.8±12.2</td>
<td>22.8±10.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>PVR, dyne·s·cm⁻⁵</td>
<td>592±270</td>
<td>217±160</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

+Associated Medical Conditions indicates patients with associated medical conditions; −Associated Medical Conditions, patients without associated medical conditions; and PAP, pulmonary arterial pressure.
our patient cohort, PEA was performed in 105 subjects (58%), all of whom fulfilled strict surgical criteria. These patients had a clear survival benefit compared with unoperated patients (hazard ratio, 0.14; 95% CI, 0.05 to 0.41; \( P=0.0003 \)). The younger age of PEA patients (52±15 versus 64±15 years; \( P<0.0001 \)) does not explain the survival benefit because age was not a systematic predictor of long-term survival in the overall cohort (hazard ratio, 1.00; 95% CI, 0.98 to 1.02; \( P=0.72 \)). PEA resulted in significant hemodynamic improvement, which has been shown to be a predictor of long-term postoperative survival.\(^{10}\)

There are several limitations and questions raised by the present study. A main limitation of the present study is its retrospective observational design. Furthermore, the surgical classification proposed by Thistlethwaite et al\(^ {18} \) is a postoperative classification with limited value in risk stratification of unoperated patients. Indeed, patients with associated medical conditions were classified largely as CTEPH types 1 to 3 and yet had a poor outcome. When the adjusted hazard ratios for these factors are compared, it appears that the presence of associated medical conditions is of higher prognostic relevance than CTEPH type (Table 3: 3.17 [95% CI, 1.70 to 5.92] versus 1.13 [95% CI, 0.50 to 2.55]). This is not in contradiction to data published by Jamieson et al\(^ {15} \) who studied the effect of CTEPH type on perioperative mortality but not on long-term outcome.

The mechanisms of worse outcome in patients with associated medical conditions remain undefined. The presence of associated medical conditions was not by itself the cause of death in any patient. Given similar baseline hemodynamics (Table 4) and similar durations of total circulatory arrest in patients with associated medical conditions and patients without associated medical conditions undergoing PEA, it is also unlikely that a higher degree of right ventricular dysfunction in these patients explains increased postoperative PVR. To avoid any bias potentially imposed by the surgical intervention, we analyzed patients not suitable for PEA, in whom the observed outcome reflects the natural course of the disease. In these patients, the presence of associated medical conditions was the only predictor of death from right heart failure or lung transplantation. Secondary small-vessel arteriopathy in CTEPH has been recognized and labeled as a negative predictor for operative survival.\(^{20}\) We speculate that a higher degree of secondary pulmonary vasculopathy in patients with associated medical conditions accounts for worse outcomes. In the absence of standardized methods to accurately detect the presence or assess the degree of small-vessel involvement in patients with CTEPH, it will be difficult to prove that patients with associated medical conditions suffer from a greater degree of small-vessel disease. Some weak evidence comes from pathological lung specimens of those patients with a history of splenectomy who were eligible for PEA\(^ {16} \) that demonstrated a significant degree of small-vessel pulmonary arteriopathy. The biological mechanisms leading to small-vessel arteriopathy remain unclear. Inflammation has been shown to be involved in the pathogenesis of some types of pulmonary vascular disease, including monocrotaline-induced pulmonary hypertension in rats and PAH of various origins in humans, such as connective tissue diseases and human immunodeficiency virus infection.\(^ {21} \) Previously, we have proposed that thrombus infection may be an important stimulus for excessive vascular remodeling and the development of secondary vascular changes.\(^ {13} \)

### Conclusion

The present report shows that medical conditions that have been previously identified as risk factors for CTEPH are associated with increased mortality and unfavorable outcome after PEA. Patients with associated medical conditions represent a distinct subentity of CTEPH, potentially requiring more aggressive presurgical as well as perioperative and postsurgical vasodilator treatment.

### Sources of Funding

This research was supported by the Austrian fellowship grants Fonds zur Förderung der wissenschaftlichen Forschung P13834-MED and S9406-B11 (to Dr Lang), Österreichischer Herzfonds (to Dr Bonderman), Österreichischer Selbsthilfeverein Lungenhochdruck, and the Ludwig Boltzmann Institute for Cardiovascular Research.

### Disclosures

None.

### References


**CLINICAL PERSPECTIVE**

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension that can be potentially cured by surgical pulmonary endarterectomy of major, lobar, and segmental pulmonary arterial branches. However, it has been recognized that the disorder may be accompanied by small-vessel pulmonary arteriopathy that is associated with perioperative death, postoperative pulmonary hypertension, or recurrence of disease. In our work, we have identified a subset of patients with chronic thromboembolic pulmonary hypertension characterized by major-vessel pulmonary arterial obstruction in the presence of associated medical conditions (defined as previous splenectomy, indwelling central catheters, and chronic inflammatory conditions), who are at an increased risk for death and recurrent pulmonary hypertension after pulmonary endarterectomy. Our data lay the groundwork for potential early stratification of patients with chronic thromboembolic pulmonary hypertension to optimize candidacy for surgical as opposed to alternative, eg, pharmacological, treatments.
Predictors of Outcome in Chronic Thromboembolic Pulmonary Hypertension
Diana Bonderman, Nika Skoro-Sajer, Johannes Jakowitsch, Christopher Adlbrecht, Daniela Dunkler, Sharokh Taghavi, Walter Klepetko, Meinhard Kneussl and Irene M. Lang

Circulation. 2007;115:2153-2158; originally published online April 9, 2007;
doi: 10.1161/CIRCULATIONAHA.106.661041
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/115/16/2153

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/