Patent Foramen Ovale Is an Important Predictor of Adverse Outcome in Patients With Major Pulmonary Embolism

Stavros Konstantinides, MD; Annette Geibel, MD; Wolfgang Kasper, MD; Manfred Olschewski, MD; Liane Blümel, MD; Hanjörg Just, MD

Background—Right-to-left shunt through a patent foramen ovale is frequently diagnosed by contrast echocardiography and can be particularly prominent in the presence of elevated pressures in the right side of the heart. Its prognostic significance in patients with pulmonary thromboembolism, however, is unknown.

Methods and Results—The present prospective study included 139 consecutive patients with major pulmonary embolism diagnosed on the basis of clinical, echocardiographic, and cardiac catheterization criteria. All patients underwent contrast echocardiography at presentation. The end points of the study were overall mortality and complicated clinical course during the hospital stay defined as death, cerebral or peripheral arterial thromboembolism, major bleeding, or need for endotracheal intubation or cardiopulmonary resuscitation. Patent foramen ovale was diagnosed in 48 patients (35%). These patients had a death rate of 33% as opposed to 14% in patients with a negative echo-contrast examination ($P = .015$). Logistic regression analysis demonstrated that the only independent predictors of mortality in the study population were a patent foramen ovale (odds ratio [OR], 11.4; $P < .001$) and arterial hypotension at presentation (OR, 26.3; $P < .001$). Patients with a patent foramen ovale also had a significantly higher incidence of ischemic stroke (13% versus 2.2%; $P = .02$) and peripheral arterial embolism (15 versus 0%; $P < .001$). Overall, the risk of a complicated in-hospital course was 5.2 times higher in this patient group ($P < .001$).

Conclusions—In patients with major pulmonary embolism, echocardiographic detection of a patent foramen ovale signifies a particularly high risk of death and arterial thromboembolic complications. (Circulation. 1998;97:1946-1951.)

Key Words: embolism ■ echocardiography ■ contrast media ■ shunts

The clinical relevance of a patent foramen ovale (PFO), a relatively frequent remnant of fetal circulation, has remained obscure for many decades. Before the development of echocardiographic imaging techniques, detection of PFO during life and clinical diagnosis of paradoxical embolism were confined to isolated reports. During the past 15 years, the initial studies reporting noninvasive detection of right-to-left atrial shunt by contrast echocardiography were followed by extensive clinical research on the association between PFO and cryptogenic stroke. However, none of the major series provided data on those patients who would be expected to be at particularly high risk of paradoxical embolism, namely patients with elevated pressures in the right side of the heart caused by acute major pulmonary embolism. In a previously published report, we observed that the presence of a PFO in this patient group was associated with a high incidence of cerebral and peripheral ischemic events suggestive of paradoxical embolism. Therefore, the aim of the present prospective study was to test the hypothesis that PFO detected by contrast echocardiography is an important prognostic indicator, especially with regard to mortality and the occurrence of cardiovascular complications during the acute phase of pulmonary embolism.

Methods

Study Population

Between May 1988 and December 1994, 1343 consecutive patients with clinically suspected acute pulmonary embolism either on admission or during the hospital stay prospectively underwent two-dimensional and Doppler echocardiographic evaluation at our institution as part of the initial diagnostic workup. Of these, 139 patients who were found to have acute major pulmonary embolism formed the population of the present study.

The diagnosis of acute major pulmonary embolism was based on clinical suspicion of pulmonary embolism as defined below in combination with at least one of the following criteria: (1) echocardiographic findings indicating acute pressure overload in the right side of the heart in the absence of mitral valve or left ventricular disease and/or (2) echocardiographic evidence of pulmonary hypertension or diagnosis of precapillary pulmonary hypertension on catheterization of the right side of the heart. Nuclear imaging studies (ventilation-perfusion lung scans) or pulmonary angiograms were...
performed in all patients whose condition was considered stable enough to permit their transportation from the emergency room or intensive care unit.

For clinical suspicion of acute pulmonary embolism, three or more of the following findings had to be present: (1) syncope, (2) tachycardia (heart rate >100 bpm), (3) dyspnea and/or tachypnea (breathing rate over 24 breaths per minute or need for mechanical ventilation), (4) arterial hypoxemia (partial pressure of oxygen <70 mm Hg while breathing room air or <80 mm Hg under supplemental oxygen of ≥2 L/min), (5) new-onset ECG signs of strain in the right side of the heart (complete or incomplete right bundle-branch block), S waves in lead I combined with Q waves in lead III, or T-wave inversion in the precordial leads V1 through V3. Echocardiographic detection of acute right ventricular pressure overload was based on the presence of (1) a dilated right ventricle (end-diastolic diameter ≥30 mm measured from the parasternal short-axis view or a right ventricle appearing larger than the left ventricle from the apical or subcostal four-chamber view) or (2) right ventricular hypertrophy (free wall thickness >5 mm as measured from the parasternal short-axis or the subcostal four-chamber view) together with an elevation of right atrial pressure (absence of inspiratory collapse of the inferior vena cava).

The presence of pulmonary hypertension had to be confirmed by at least one of the following findings: (1) dilation of the right pulmonary artery, defined as cross-sectional diameter >12 mm/m² body surface area on the suprasternal echocardiogram, (12) tricuspid regurgitant jet velocity of ≥2.5 m/s on Doppler echocardiography in the absence of inspiratory collapse of the inferior vena cava, (13) or (3) diagnosis of precapillary pulmonary hypertension on catheterization of the right side of the heart (systolic pulmonary arterial pressure ≥35 mm Hg or mean pressure ≥20 mm Hg in the presence of normal pulmonary artery occlusion pressure).

The tricuspid regurgitant jet velocity obtained by continuous-wave Doppler echocardiography was used to estimate systolic right ventricular pressure by means of the simplified Bernoulli equation. (12) Invasive measurement of right atrial, right ventricular, and pulmonary artery pressures was performed by means of a Swan-Ganz thermomodule catheter. Finally, scintigraphic confirmation of pulmonary embolism (ie, definition of a diagnostic or high-probability lung scan) was based on the criteria described by Selby et al. (13)

### Contrast Echocardiography and the Diagnosis of a PFO

All patients in the study population underwent contrast echocardiographic studies during the initial ultrasound examination for detection of right-to-left shunt through a PFO. During visualization of the heart from the apical four-chamber view, echo-contrast opacification of the right atrium was achieved by rapidly injecting 10 mL of agitated 5.5% oxypolygelatine solution (Gelifundol, Biotest Pharma Inc) through an antecubital vein as previously described. (14) Every care was taken to extrude all macroscopic air from the syringe before injection. Echo-contrast was considered to be adequate if the entire right atrium remained opacified for at least three cardiac cycles. The detection of five or more microbubbles in the left heart cavities within three cardiac cycles after their appearance in the right atrium was considered diagnostic of a PFO. (14) Informed consent was obtained from all patients or their first-degree relatives before administration of the echo-contrast agent. The procedure was well tolerated in all cases, and no side effects were reported.

### Definition of Clinical End Points

Statistical evaluation of the patients’ outcome during the in-hospital period focused on two major clinical end points: overall mortality and complicated in-hospital course, defined as the occurrence of one of the following events: death, ischemic stroke, peripheral arterial embolism, major bleeding, or the need for endotracheal intubation or cardiopulmonary resuscitation. The diagnosis of ischemic stroke was confirmed by CT or autopsy in all cases. The diagnosis of peripheral arterial embolism was based on clinical, laboratory, and radiological findings signifying vascular occlusion with renal, intestinal, or limb ischemia. Finally, major bleeding was defined as hemorrhagic stroke confirmed by CT or autopsy or as a bleeding episode that fulfilled at least one of the following criteria: a decrease in hemoglobin levels of ≥2 g/dL, requirement for a blood transfusion of two units or more, retroperitoneal bleeding, or bleeding that required surgical intervention or discontinuation of heparin anticoagulation or thrombolytic treatment.

### Statistical Analysis

For descriptive purposes, quantitative variables are presented as mean±SD; qualitative variables, as absolute and relative frequencies. The prognostic relevance of PFO and other clinically important variables with respect to mortality and major in-hospital events was analyzed univariately by Fisher’s exact test. To investigate whether the prognostic effect of PFO is independent of other clinical variables, a multiple logistic regression model was additionally applied to the two major end points (mortality and complicated in-hospital course). The results of the logistic regression models are presented as estimated odds ratios (ORs) with the corresponding 95% confidence intervals. All significance tests were two-sided, with a value of P<.05 considered to indicate clinical significance. Data processing and analysis were performed with the Statistical Analysis System.

### Results

#### Clinical and Echocardiographic Findings at Diagnosis

The study population consisted of 69 women and 70 men with a mean age of 59±17 years (range, 17 to 89 years); their clinical characteristics at the time of diagnosis are shown in Table 1. Twenty-three patients (17%) had no known risk factors for venous thromboembolic disease in their histories. Most patients (70%) presented with an acute onset of symptoms, ie, <5 days before the diagnosis of pulmonary embolism. All patients had evidence of pulmonary hypertension and/or right ventricular pressure overload according to the aforementioned criteria. Right ventricular dilation was present in the vast majority of the patients (134, or 96% of the

### TABLE 1. Clinical Characteristics at Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute symptom onset (within 4 d)</td>
<td>97 (70)</td>
</tr>
<tr>
<td>Syncope</td>
<td>35 (25)</td>
</tr>
<tr>
<td>Focal neurological deficit(s)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Peripheral arterial occlusion*</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Arterial hypotension (systolic blood pressure &lt;90 mm Hg)</td>
<td>118 (85)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>Recent major surgery (within 14 d)</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Recent major trauma or fracture (within 14 d)</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>History of venous thrombosis</td>
<td>45 (32)</td>
</tr>
<tr>
<td>History of pulmonary embolism</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Gestation</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (2.1)</td>
</tr>
</tbody>
</table>

n=139.

*Clinical and laboratory findings signifying renal, intestinal, or limb ischemia.
study population). In addition, echocardiography detected the presence of thrombi in the right chambers or in the proximal portions of the right pulmonary artery in 25 patients (18%). After the initial clinical and echocardiographic evaluation, nuclear imaging and pulmonary angiographic studies confirmed the diagnosis of pulmonary embolism in 86 (62%) and 32 (23%) patients, respectively. Overall, confirmation of the thromboembolic event was provided by at least one of these methods or by the autopsy findings in 110 patients of the study group (79%). B-mode and/or Doppler ultrasonographic or phlebographic studies were performed in 105 patients (76%) and revealed the presence of deep vein thrombosis in 77 of these patients (73%).

Pulmonary artery pressure was measured during bedside catheterization of the right side of the heart in 61 patients (44%). In 93 patients (67%), systolic right ventricular pressure (approximately equal to pulmonary artery pressure) was noninvasively estimated by Doppler echocardiography as described in “Methods.” Overall, the severity of pulmonary hypertension could be assessed at the bedside by either of these two methods in 112 patients (81%). In these patients, systolic pulmonary artery pressure ranged between 32 and 110 mm Hg (mean, 57±18 mm Hg). The good correlation between invasively and echocardiographically obtained pulmonary artery pressures as reported by other investigators12 has been confirmed in our laboratory for patients with pulmonary embolism.10

Right-to-left shunt through a PFO was diagnosed by contrast echocardiography in 48 patients of the study population (35%; see the Figure). There was no difference in systolic pulmonary pressure between the patients with and without PFO (58±17 versus 57±19 mm Hg; P=.60).

After diagnosis of acute pulmonary embolism, 57 patients (41%) were treated with thrombolytic agents according to the judgment of the clinicians in the emergency room or intensive care unit. The remaining 82 patients (59%) received conventional heparin anticoagulation. Thrombolytic treatment was given to 22 patients with and 35 patients without PFO (46% versus 38%; P=.47).

Predictors of In-Hospital Mortality

The mean duration of hospitalization after the diagnosis of acute pulmonary embolism was 22±17 days. During this period, 29 patients (21% of the study population) died. Death was directly related to the acute thromboembolic event in the vast majority of the cases (25 of the 29 patients; 86%). One patient died of septic shock on the fourth postoperative day after emergency pulmonary embolectomy. Another patient recovered from the initial episode of pulmonary embolism but died of recurrent major pulmonary embolism 3 days after presentation. Finally, in-hospital death was due to the underlying disease in 2 patients who had Salmonella osteomyelitis with sepsis and a malignant tumor, respectively.

Univariate analysis revealed that in-hospital mortality was more than twice as high in the presence of PFO (33% versus 14% in patients without atrial communication; P=.015). Death during the in-hospital phase was also significantly more frequent in patients with an acute onset of symptoms related to pulmonary embolism (27% versus 7.1%; P=.01)

and in those presenting with cardiogenic shock caused by failure of the right side of the heart (52% versus 15%; P<.001). Logistic regression analysis demonstrated that after adjustment for the baseline clinical characteristics listed in Table 1 and for the echocardiographic detection of right-side thrombi, PFO and arterial hypotension remained the only independent predictors of in-hospital death (OR, 11.4 and
TABLE 2. Determinants of Outcome in Patients With Acute Major Pulmonary Embolism

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Overall In-Hospital Mortality OR (95% CI)</th>
<th>Complicated In-Hospital Course* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient foramen ovale</td>
<td>11.35 (2.89–44.52) &lt;.001</td>
<td>5.21 (2.32–11.71) &lt;.001</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
<td>1.28 (0.45–3.66) &lt;.04</td>
<td>1.46 (0.67–3.19) &lt;.04</td>
</tr>
<tr>
<td>Acute symptom onset</td>
<td>3.72 (0.88–15.72) &lt;.07</td>
<td>0.91 (0.40–2.09) &lt;.04</td>
</tr>
<tr>
<td>Arterial hypotension</td>
<td>26.29 (5.76–120) &lt;.001</td>
<td>7.57 (2.10–27.26) &lt;.001</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3.05 (0.46–19.83) &lt;.24</td>
<td>6.09 (0.62–59.6) &lt;.12</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>2.31 (0.53–10.17) &lt;.27</td>
<td>1.52 (0.46–5.05) &lt;.50</td>
</tr>
<tr>
<td>Right heart or proximal PA thrombi (echocardiography)</td>
<td>1.70 (0.49–5.95) &lt;.41</td>
<td>1.06 (0.36–3.05) &lt;.93</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; BP, blood pressure; and PA, pulmonary artery.

*Complicated in-hospital course was defined as the occurrence of one of the following events: death, ischemic stroke, peripheral arterial embolism, major bleeding, or the need for endotracheal intubation or cardiopulmonary resuscitation.

26.3, respectively; Table 2), PFO remained a significant independent predictor of mortality even if only those patients with definite confirmation of pulmonary embolism by lung scan, pulmonary angiography, or autopsy were included in the statistical analysis (OR, 8.58; 95% confidence interval, 1.92 to 38.4).

Patients with severe pulmonary hypertension (systolic pressure >60 mm Hg) had a mortality rate of 10.3% compared with 23.3% in patients with mild or moderate pulmonary hypertension (systolic pressure, 32 to 60 mm Hg; P=.13). On multivariate analysis, the association between pulmonary artery pressure and the risk of in-hospital death reached marginal statistical significance in the whole study population (OR, 3.6:1 for mild to moderate hypertension; P=.10). On the other hand, death risk was independent of the severity of pulmonary hypertension in patients with right-to-left shunt through a PFO (P=.50).

Major Clinical Events and Determinants of a Complicated In-Hospital Course

Following diagnosis of acute major pulmonary embolism, 62 patients (45%) suffered at least one of the major in-hospital clinical events listed in Table 3. Ischemic stroke occurred in 8 patients (5.8%), and 7 patients (5%) suffered a peripheral arterial thromboembolic event. Major bleeding was documented in 30 patients (22%), and the occurrence of cerebral bleeding was 2.1%. The frequency of major bleeding episodes was 32% among 57 patients (41%) of the study group who received thrombolytic treatment as opposed to 15% in the remaining 82 patients who underwent conventional heparin anticoagulation (P=.02).

PFO was found to be significantly associated with the occurrence of ischemic stroke, peripheral arterial embolism, and the need for endotracheal intubation (Table 3). In fact, the presence of a PFO resulted in a more than fivefold increase in the adjusted risk of major in-hospital complications (P<.001; Table 2).

Discussion

Since its first description by Cohnheim in 1877, the entity of paradoxical embolism through a PFO has remained a diagnostic challenge. Definite confirmation of paradoxical embolism essentially requires the detection of a right atrial thrombus crossing the foramen ovale. However, direct observation of this phenomenon during life is rarely possible and remains confined to isolated echocardiographic reports. In clinical practice, the diagnosis of paradoxical embolism is almost always presumptive and relies on (1) the occurrence of an arterial thromboembolic event in the absence of atrial fibrillation, disease of the left side of the heart, or severe atherosclerosis of the thoracic aorta; (2) the detection of right-to-left shunt, usually through a PFO or an atrial septal defect; and (3) the presence of venous thrombosis or pulmonary embolism.

In recent years, contrast transthoracic or transesophageal echocardiography was established as a simple, accurate, and safe procedure for the diagnosis of interatrial communication. Several studies reported a significant association between echocardiographically detected PFO and the occurrence of cryptogenic stroke. On the other hand, it is not entirely clear whether deep vein thrombosis or pulmonary embolism was also present in the patients of those series. Thus, the clinical importance of a PFO still continues to be the subject of debate.

Transient right-to-left shunt through a PFO can, indeed, occur even in the presence of normal right-side hemodynamics. However, this phenomenon becomes especially prominent in the setting of elevated right-side pressures. We therefore hypothesized that patients with major pulmonary embolism and PFO might be particularly prone to suffer paradoxical embolism with a substantial impact on their in-hospital morbidity and mortality. In the present prospective study, we investigated the death rate and the incidence of arterial thromboembolic events in a patient population presenting with acute major pulmonary embolism. All patients underwent contrast echocardiographic imaging at diagnosis.

TABLE 3. In-Hospital Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients With Patent Foramen Ovale (n=48), n (%)</th>
<th>Patients Without Patent Foramen Ovale (n=91), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>6 (13)</td>
<td>2 (2.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Peripheral arterial embolism</td>
<td>7 (15)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>2 (4.2)</td>
<td>1 (1.1)</td>
<td>.27</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>8 (17)</td>
<td>19 (21)</td>
<td>.66</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>17 (35)</td>
<td>15 (16)</td>
<td>.02</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>9 (19)</td>
<td>10 (11)</td>
<td>.3</td>
</tr>
<tr>
<td>Death</td>
<td>16 (33)</td>
<td>13 (14)</td>
<td>.015</td>
</tr>
</tbody>
</table>
The results of the study provide a clear confirmation of our hypothesis. The death rate of patients with PFO was as high as 33% and more than twice as high as that of patients without evidence of right-to-left atrial shunt. According to multivariate analysis, PFO was associated with more than a 10-fold increase in death risk and a 5-fold increase in the risk of major adverse events during the hospital stay. The clinical relevance of these findings is emphasized by the high frequency of PFO in our study patients (35%), which is in accordance with the results of autopsy series.

The overall mortality rate of our patient population was 21%, and the frequency of serious in-hospital complications, such as arterial thromboembolism, major bleeding, need for endotracheal intubation, or cardiopulmonary resuscitation, was also very high (45%). These figures are not surprising in view of the fact that the present study focused on patients with major pulmonary embolism. Our inclusion criteria required echocardiographic evidence of acute right ventricular pressure overload and/or pulmonary hypertension diagnosed by echocardiography or catheterization of the right side of the heart. Definite confirmation of acute pulmonary embolism by scintigraphic or pulmonary angiographic studies was recommended by the study protocol but not defined as an inclusion criterion. Because clinical and hemodynamic instability precluded the performance of these procedures in 21% of our patients, diagnostic uncertainty remains a possibility in some cases. In particular, it cannot be excluded that preexisting pulmonary hypertension (resulting from recurrent thromboembolism or chronic pulmonary disease) might have led to right ventricular pressure overload in some patients. The differential diagnosis of an enlarged right ventricle also includes right ventricular myocardial infarction and congenital heart disease. These limitations notwithstanding, a diagnostic strategy based on echocardiography not only is safe and practicable in the intensive or emergency care setting but also can lead to rapid identification and probably to more effective treatment of high-risk patients with acute pulmonary embolism.

We found that systolic pulmonary pressure $>60$ mm Hg was associated with a tendency toward decreased mortality rates compared with mild or moderate pulmonary hypertension. The explanation for this finding probably lies in the fact that severe pulmonary hypertension signifies the presence of chronic right ventricular pressure overload as previously demonstrated. In a recent study, we could show that patients with a chronically “adapted,” hypertrophied right ventricle resulting from recurrent thromboembolic events could better tolerate the hemodynamic consequences of pulmonary embolism during the acute phase.

Conclusions

The results of the present prospective study have, in our opinion, important clinical implications. They demonstrate that right-to-left shunt through a PFO is an independent predictor of adverse outcome in patients with acute major pulmonary embolism. Thus, detection of PFO by contrast echocardiography should probably prompt consideration of aggressive therapeutic options, such as thrombolytic treatment or catheter thrombus fragmentation, to restore pulmonary vascular patency and normalize right-side hemodynamics as soon as possible. On the other hand, silent paradoxical embolism might increase the risk of life-threatening hemorrhagic complications of thrombolysis. These crucial issues need to be addressed by future controlled trials and will, it is hoped, lead to a more sophisticated and effective strategy in the treatment of acute pulmonary embolism.

References


22. Hales CA, Johnson RA. Pulmonary thromboembolism and non-thromboembolic pulmonary vascular disease. In: Eagle KA, Haber E,


Patent Foramen Ovale Is an Important Predictor of Adverse Outcome in Patients With Major Pulmonary Embolism
Stavros Konstantinides, Annette Geibel, Wolfgang Kasper, Manfred Olschewski, Liane Blümel and Hanjörg Just

_Circulation_. 1998;97:1946-1951
doi: 10.1161/01.CIR.97.19.1946

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 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/97/19/1946

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/