Diagnostic Value of Pericardial Biopsy
Improvement With Extensive Sampling Enabled by Pericardioscopy

Petar M. Seferović, MD, PhD, FESC; Arsen D. Ristić, MD, FESC; Ružica Maksimović, MD, PhD; Vujadin Tatić, MD, PhD; Miodrag Ostojić, MD, PhD, FESC; Vladimir Kanjuh, MD, PhD

Background—The clinical significance of pericardial biopsy is controversial. The aim of this study was to assess the feasibility and diagnostic value of 3 approaches to pericardial biopsy: fluoroscopic control and standard sampling, pericardioscopy guidance with standard sampling, and pericardioscopy guidance with extensive sampling.

Methods and Results—Forty-nine subsequent patients with a large pericardial effusion underwent parietal pericardial biopsy. In group 1 (12 patients, 66.7% males, age 46.7 ± 12.2 years), pericardial biopsy was guided by fluoroscopy (3 to 6 samples per patient). Group 2 included 22 patients (50% males, age 50.8 ± 10.4 years) undergoing 4 to 6 pericardial biopsies per patient guided by pericardioscopy (16F flexible endoscope). In group 3, extensive pericardial sampling was performed, guided by pericardioscopy (15 patients, 53.3% males, age 53.7 ± 12.8 years, 18 to 20 samples per patient). Sampling efficiency was better with pericardioscopy (group 2, 84.9%; group 3, 84.2%) compared with fluoroscopic guidance (group 1, 43.7%; P < 0.01). Diagnostic value was defined as a new diagnosis uncovered, etiology revealed, clinical diagnosis confirmed, and the biopsy false-negative. Pericardial biopsy in group 3 had higher diagnostic value than in group 1 in revealing new diagnosis (40% versus 8.3%, P < 0.05) and etiology (53.3% versus 8.3%, P < 0.05). In group 2, pericardial biopsy had a higher yield in establishing etiology than in group 1 (40.9% versus 8.3%; P < 0.05). Pericardial biopsy was false-negative in 58.3% in group 1 in contrast to 6.7% in group 3 (P < 0.01). There were no major complications.

Conclusions—Pericardioscopic guidance enhanced pericardial sampling efficiency. The diagnostic value of pericardial biopsy was significantly improved by extensive sampling made possible by pericardioscopy. (Circulation. 2003;107:978-983.)

Key Words: biopsy ■ diagnosis ■ pericarditis ■ pericardium

Pericardial biopsy has opened a new perspective for establishing the etiology of pericardial diseases. However, its diagnostic value has been reported as unsatisfactory.1,2 Technical advances in instrumentation3 and introduction of pericardioscopy4-8 have improved the diagnostic yield. Several studies have confirmed the diagnostic value of targeted pericardial biopsy guided by surgical pericardioscopy.7-9 Other investigators have reported clinically relevant results using flexible percutaneous pericardioscopy to guide epicardial biopsies2,5,6 and emphasized its diagnostic superiority in comparison with parietal pericardial biopsy. However, none of the previous studies implemented endoscopic guidance to obtain a very large number of samples, reducing the sampling error inherent to all biopsy procedures.10

The aim of this study was to analyze the feasibility and diagnostic value of 3 approaches to pericardial biopsy: fluoroscopic control and standard number of pericardial samples, pericardioscopy guidance with standard sampling, and pericardioscopy guidance with extensive sampling.

Methods

Patients

The study population included 49 patients with large pericardial effusions diagnosed by echocardiography (>2 cm in diastole, in front of the right ventricle, 4-chamber view). In 14 of 49 patients, malignant disease had been previously diagnosed (5 lung cancers, 5 breast cancers, 2 Hodgkin’s diseases, 1 plasmocytoma, and 1 synoviosarcoma). Nine patients had acute pericarditis; 14 were referred in the subacute stage and 26 in the chronic stage of the disease. Ten patients presented with a relapse of pericardial effusion after previous pericardiocenteses, but in none had the etiology of the disease been revealed by cytology. Patients with coagulation disorders, effusive-constrictive pericarditis, and advanced respiratory insufficiency were excluded. The local ethics committee approved the study, and all patients signed an informed-consent form.

Design of the Study

After the initial clinical workup, including chest-x ray and echocardiography, patients were subsequently assigned to pericardial biopsy using 3 different approaches (Table 1). Only the biopsies of the parietal pericardial layer were performed, whereas no visceral
(epicardial) biopsies were taken. In group 1 (12 patients, 66.7% males, mean age 46.7±12.2 years), pericardial biopsy was guided by fluoroscopy (3 to 6 samples per patient). Group 2 included 22 patients (50% males, mean age 50.8±10.4 years) undergoing 4 to 6 biopsies per patient guided by pericardioscopy. In group 3, extensive pericardial sampling was performed using identical type of endoscope (15 patients, 53.3% males, mean age 53.7±12.8 years, 18 to 20 samples per patient). Extensive pericardial sampling (group 3) targeted by pericardioscopy was introduced after the initial experience with standard sampling (group 2) to reduce the sampling error.

Subxiphoid pericardiotomies and pericardial biopsy were performed in the same session in all patients in group 1. In groups 2 and 3, pericardioscopy and pericardial biopsy were postponed for 1 or 2 days in 11 of 37 patients to obtain complete drainage of hemorrhagic effusions. Pericardial fluid cytology was performed in all patients by an experienced pathologist. Chest x-ray and echocardiography were repeated 24 to 48 hours after the procedure and at discharge. Patients were followed-up by echocardiography every 30 days for the first 3 months and every 3 to 6 months afterward.

Pericardial Biopsy With Fluoroscopy Control

The procedures were performed in the cardiac catheterization laboratory, in local anesthesia, after pericardiotomies. After evacuation of the pericardial effusion, 200 mL of 37 °C warm saline was injected intrapericardially to enable safe biopsy. Using the already-introduced pericardial drainage catheter, a standard 0.038” J-tip guidewire was placed into the pericardial space. Subsequently, the guidewire, additional dilations were performed and a 7F sheath was positioned on the left lateral surface of the pericardium (Figure 1). For the proper orientation, 5 to 10 mL of angiographic contrast was injected intrapericardially. To perform pericardial biopsy, Olympus FB43-ST fenestrated forceps with central needle was used, and 3 to 6 samples were taken from the lateral surface of the parietal pericardium in the posterior-anterior angiographic view (Figure 2).

After the procedure, the sheath was exchanged for a 7F pigtail catheter for evacuation of the residual fluid. The catheter was left in the pericardial space until the fluid production decreased to <100 mL/day.

Pericardial Biopsy Targeted by Pericardioscopy

Having in mind the advantages and drawbacks of various devices used in other centers,4–7 we selected for the present study an Olympus HYF-1T (Olympus Co), 16F flexible endoscope (interventional hysterosalpingoscope) with a working channel of 2.2 mm. All procedures were performed in the cardiac catheterization laboratory under local anesthesia.

Preparation for percutaneous flexible pericardioscopy includes gradual dilation of the skin, subcutaneous tissue, and parietal pericardium (9F, 12F, 14F, and 16F) over the 0.038” guidewire. After positioning of the 16.5F introducer set, dilator is removed and the flexible endoscope is introduced through the sheath, inside pericardial cavity. Using rotation and flexion of the distal tip of the instrument, inspection of the pericardium is performed and several targeted parietal biopsies are taken.

Several modifications of previously reported techniques for flexible percutaneous pericardioscopy have been introduced in our institution.11 In the first 3 patients, the procedure was performed after replacing the pericardial effusion with warm normal saline (37 °C), as described previously.2,3,4 However, because visualization was often unclear, a vacuum pump (Keymed SSU-2) was applied to remove the entire effusion.

In patients with hemorrhagic effusion (16 of 37) 100- to 150-mL aliquots of normal saline were repeatedly injected and removed until the fluid from the pericardial sac was clear. In 5 of 16 patients, this maneuver provided adequate visualization. To improve visibility, in

| Table 1. Baseline Characteristics of Patients Undergoing Pericardial Biopsy |
|---------------------|----------------|--------------------|-----------------|-----------------|
| Patients No. | Males, % | Mean Age, y | Evacuated Pericardial Effusion, mL | Pericardial Biopsy Guidance | Samples per Patient |
| Group 1 | 12 | 66.7 | 46.7±12.2 | 775.0±171.2 | Fluoroscopy | 3–6 |
| Group 2 | 22 | 50.0 | 50.8±10.4 | 769.5±185.7 | Pericardioscopy | 4–6 |
| Group 3 | 15 | 53.3 | 53.7±12.8 | 790.0±204.6 | Pericardioscopy | 18–20 |

Figure 1. Pericardial biopsy using fluoroscopy control. Frontal view with magnification. Olympus FB43-ST fenestrated forceps with central needle is protruding from the 7F 23-cm-long sheath. Biopsy is about to be taken from the inferolateral parietal pericardium.

Figure 2. Flexible percutaneous pericardioscopy with aimed parietal pericardial biopsy. Fluoroscopic frontal view. Olympus FB43-ST biopsy forceps (fenestrated with the central needle) is protruding from the working channel of the endoscope.
TABLE 2. Feasibility of Pericardial Biopsy Performed With FB-43ST Biopsy Forceps

<table>
<thead>
<tr>
<th>Olympus FB-43ST Biopsy Forceps</th>
<th>Group 1 (12 Patients)</th>
<th>Group 2 (22 Patients)</th>
<th>Group 3 (15 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluoroscopy</td>
<td>Pericardioscopy</td>
<td>Pericardioscopy</td>
</tr>
<tr>
<td></td>
<td>3–6 Samples</td>
<td>4–6 Samples</td>
<td>18–20 Samples</td>
</tr>
<tr>
<td>Feasibility of pericardial access, %</td>
<td>92.8</td>
<td>96.2</td>
<td>100</td>
</tr>
<tr>
<td>Feasibility of sheath introduction, %</td>
<td>92.3</td>
<td>96.0</td>
<td>100</td>
</tr>
<tr>
<td>Adequate pericardial visualization, %</td>
<td>NA</td>
<td>90.9</td>
<td>93.3</td>
</tr>
<tr>
<td>Sampling efficiency, %</td>
<td>43.7</td>
<td>84.9*</td>
<td>84.2†</td>
</tr>
<tr>
<td>Total number of pericardial samples</td>
<td>62</td>
<td>129</td>
<td>289</td>
</tr>
<tr>
<td>Mean sample number</td>
<td>5.2±1.0</td>
<td>5.9±0.5</td>
<td>19.3±1.0</td>
</tr>
<tr>
<td>Total number of biopsy attempts</td>
<td>142</td>
<td>152</td>
<td>343</td>
</tr>
<tr>
<td>Mean number of biopsy attempts</td>
<td>11.8±2.1</td>
<td>6.9±0.8</td>
<td>22.9±2.2</td>
</tr>
</tbody>
</table>

Sampling efficiency indicates successful biopsies per total number of attempts (%).

ANOVA results: F=5.43, P<0.01; *P<0.01 group 2 vs group 1; †P<0.01 group 3 vs group 1.

Results are given as absolute numbers and mean±SD or frequencies (%). Continuous and categorical variables were compared using the Student’s t test and χ² or ANOVA when appropriate, respectively. Statistical significance was considered with P<0.05. The analysis was performed in SPSS 10.0 for Windows.

Data Analysis

The feasibility of pericardial biopsy under fluoroscopic control included feasibility of pericardial access (92.8%), 7F-sheath introduction and positioning (92.3%), as well as sampling efficiency (43.7%). Feasibility of aimed pericardial biopsy under endoscopic control included feasibility of pericardial access (96.2% in group 2 and 100% in group 3), 16.5F sheath introduction (96.0% in group 2 and 100% in group 3), adequate pericardial visualization (90.9% in group 2 and 93.3% in group 3), and sampling efficiency (84.9% in group 2 and 84.2% in group 3) (Table 2).

Feasibility of pericardial access and sheath introduction did not differ significantly between the 3 groups. Endoscopic visualization was clearly superior when pericardial effusion was replaced with warm normal saline (37°C). Sampling efficiency was significantly better with pericardioscopy (groups 2 and 3) compared with fluoroscopic guidance (group 1) (P<0.01) (Table 2).

Predominant histopathologic findings included nonspecific inflammation (15 of 49 patients; 30.6%) and neoplastic disorders (14 of 49 patients; 28.6%) (Table 3). Tumors most often diagnosed were squamous-cell bronchogenic carcinoma

<table>
<thead>
<tr>
<th>TABLE 3. Histopathologic Findings of Pericardial Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic Findings</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Squamous-cell carcinoma, %</td>
</tr>
<tr>
<td>Adenocarcinoma, %</td>
</tr>
<tr>
<td>Mesothelioma, %</td>
</tr>
<tr>
<td>Plasmocytoma, %</td>
</tr>
<tr>
<td>Hodgkin’s disease, %</td>
</tr>
<tr>
<td>Tuberculosis, %</td>
</tr>
<tr>
<td>Nonspecific inflammation, %</td>
</tr>
</tbody>
</table>

ANOVA results (group 1 vs group 2 vs group 3): P>0.05
and adenocarcinoma. Both a new diagnosis and etiology of the disease were established by pericardial biopsy guided by fluoroscopy (group 1) in 8.3% each, clinical diagnosis was confirmed in 33.3%, and the results were false-negative (no useful information) in 58.3% of the patients. In the pericardiocentesis group with standard sampling (group 2), a new diagnosis was established in 26.3%, etiology was revealed in 40.9%, clinical diagnosis was confirmed in 36.4%, and the pericardial biopsy findings were false-negative in 36.4%. A new diagnosis in the pericardioscopy group with extensive sampling (group 3) was established in 40%, etiology was uncovered in 53.3%, clinical diagnosis was confirmed in 53.3%, and the procedure provided no useful information in only 6.7% (Figure 3).

Extensive pericardial biopsy, guided by pericardioscopy (group 3), had better diagnostic value than pericardial biopsy guided by fluoroscopy (group 1) in revealing a new diagnosis (P<0.05) and etiology of the pericardial disease (P<0.05). In group 2, pericardial biopsy had significantly higher yield in establishing etiology than in group 1 (P<0.05). Significantly lower incidence of pericardial biopsy false-negative findings occurred in group 3 compared with group 1 (P<0.01) (Figure 4).

Pericardial fluid cytology confirmed presence of neoplastic cells in a total of 10 of 18 patients (sensitivity 55.5%) with confirmed neoplastic pericardial effusion. Cytology was false-negative in 8 of 14 patients (57.1%) with positive histology findings for patients with confirmed malignant pericarditis in histology. However, in 4 patients with no confirmation of malignancy in histology, pericardial fluid cytology was positive, revealing the false-negative biopsies. The combination of false-negative histology and positive cytology occurred in group 1 (3 of 12 patients; 25%) and in group 2 (1 of 22 patients; 4.5%) but in none of 15 patients from group 3 (extensive sampling).

No major complications occurred. In groups 2 and 3, nonsustained ventricular tachycardia (2 of 37 patients; 5.4%), pain during insertion of 9F to 16.5F dilators (21 of 37 patients; 56.7%), and transient fever (13 of 37 patients; 35.1%) were noted.

**Discussion**

**Pericardial Access and Sheath Placement**

The prerequisites of pericardial biopsy feasibility are successful pericardial access and adequate visualization during pericardiocentesis. Parameters associated with unsuccessful pericardiocentesis were loculation of pericardial effusion, particularly after cardiac surgery,12–14 and massive neoplastic infiltration of the pericardium.15 Neither patients with very small nor with loculated effusion were included in our study, providing high feasibility of pericardial access (92.8% to 100%). Pericardial access failed in 2 patients in our study (1 patient from group 1 and 1 patient from group 2) because of the neoplastic pericardial infiltration.

Intrapericardial placement and adequate positioning of the pericardial biopsy sheath is another important step influencing the feasibility of the procedure. This stage failed in the present study in 4.0% to 7.7% of patients because of predominantly posterior pericardial effusion.

![Figure 4. The diagnostic value of pericardial biopsy expressed as a percentage of (1) new diagnosis (New Dg.) uncovered, (2) etiology revealed, (3) clinical diagnosis (Clin.Dg.) confirmed, and (4) false-negative (no useful information obtained). Group 1, pericardial biopsy using only fluoroscopy control; Group 2, aimed pericardial biopsy using flexible percutaneous pericardiocentesis with standard sampling; and Group 3, aimed pericardial biopsy using flexible percutaneous pericardioscopy with extensive sampling. *P<0.05.](http://circ.ahajournals.org/)

Seferović et al Pericardial Biopsy 981
Pericardial Visualization and Sampling Efficiency of Pericardial Biopsies

The advantage of optical control during the biopsy resulted in significantly higher sampling efficiency in groups 2 and 3 compared with group 1 (Table 2). Our modified approach to pericardioscopy, performed through air instead of fluid, improved the quality of the endoscopic image and made it possible to take safely numerous samples in group 3. Macroscopic view of the large areas of pericardial surface is achieved by this technique, contributing to proper selection of the biopsy site and the diagnostic value of the procedure.

Because of the elastic properties of the pericardial surface, low sampling efficiency represents a major technical issue in pericardial biopsy. It is reported to differ considerably with various bioptomes. Based on the results of our previous experimental study of the sampling efficiency, Olympus FB-43ST bioptome was applied in all patients.

Diagnostic Value of Pericardial Biopsy

Diagnostic value of pericardial biopsy was established against a composite “gold standard” comprising clinical data, imaging methods, laboratory findings, pericardial fluid cytology, and follow-up data including autopsy, if performed. However, negative pericardial histology in patients with previously established neoplastic disease was not calculated as a false-negative finding, except in patients with malignant cells in pericardial fluid cytology or neoplastic infiltration proven at necropsy. Histological diagnosis is particularly difficult in patients with malignancies and pericardial disease of nonneoplastic etiology because of the possible sampling error. Sampling error could be significantly reduced by taking large number of specimens, as shown in the present study.

Pericardial Biopsy With Fluoroscopy Control

Low diagnostic value of pericardial biopsy guided by fluoroscopy was reported by Fernandes et al, identifying the etiology of pericardial disease by pericardial biopsy in 10.5% of 38 patients, whereas in 89.5% of patients, biopsy demonstrated nonspecific chronic pericarditis. In contrast, Ziskind et al reported a favorable diagnostic value of pericardial biopsy in neoplastic pericarditis. For patients with a history of malignant disease, the adding of pericardial biopsy to pericardial fluid cytology increased the yield for obtaining the specific diagnosis from 46% to 62%. For patients without a history of malignancy, the addition of pericardial biopsy to pericardial fluid cytology increased the diagnostic yield from 7% to 29%. Larger sample volume (8F bioptome) and more aggressive sampling (6 to 8 samples from each patient) may have improved the diagnostic value. Mehan et al investigated 25 patients using angioplasty guiding catheters for pericardial biopsy guidance. Histologic diagnosis of tuberculosis pericarditis was established in 44%, purulent pericarditis was established in 8%, and nonspecific inflammatory changes were found in 48% of patients. Endrys et al reported that pericardial biopsy established the definitive diagnosis in 50% of 18 patients: tuberculosis in 6, mesothelioma in 1, and carcinoma in 2. In a pediatric population, the biopsy findings rendered an etiologic diagnosis in 63% of the cases and excluded tuberculosis and malignancy in 37%.

Targeted Pericardial Biopsy

The biopsies taken during pericardioscopy are optically targeted and therefore more selective to sample lesions. Extensive pericardial sampling applied in group 3 (sensitivity, 93.3%) provided a diagnostic value comparable to the more invasive surgical pericardioscopy (sensitivity, 92%; false-negative findings, 1.4%). Our results (partial pericardial biopsy only) were also comparable to the epicardial biopsy findings reported by Maisch et al (sensitivity, 80% in neoplastic disease and 93% in inflammatory disease). According to the same authors, pericardial biopsy results had much lower diagnostic value (neoplastic disease, 7%; inflammatory disease, 14%). These reports are also comparable to our findings for false-negative results (58.3%) taken under fluoroscopy control only (group 1).

Visceral or epicardial biopsy can be successfully targeted by pericardioscopy and potentially provide superior diagnostic value compared with partial biopsies, but it carries potentially greater risk for serious complications. No large direct comparison of the diagnostic value and safety of pericardial and epicardial biopsies was reported so far, and this issue would be valuable for additional investigation.

Targeted pericardial biopsy during pericardioscopy was shown to be particularly useful in the diagnosis of neoplastic pericarditis not only in our study but also in the experience of others. Porte et al evaluated pericardioscopic guidance using a rigid mediastinoscope (Karl Storz, Germany). Pericardial biopsies were obtained from 114 patients with a history of cancer. In 22.7%, pericardioscopy improved the results of pericardial fluid cytology and surgical pericardial biopsy (pericardial window procedure). The sensitivities of cytological studies of the pericardial fluid, pathological examinations of pericardial window biopsy, and pericardioscopic pericardial biopsies were 75%, 65%, and 97%, respectively.

The present study included 2 groups undergoing pericardioscopy-guided pericardial biopsy (groups 2 and 3) with a skewed distribution, because group 3 included the most recent patients in our series. Extensive pericardial sampling (group 3) was introduced after an interim comparison of pericardial biopsy results of group 1 and 2 demonstrated insignificant advantage of pericardioscopy, except for establishing the etiology of the disease.

Complications

Complications are a major issue in the clinical use of any invasive procedure. In our study, pericardial biopsy was not associated with any major complications. Minor complications included short runs of nonsustained ventricular tachycardia (4.7%), pain during the placement of pericardioscopy sheath (56.7%), and transient fever (35.1%). Nonsustained ventricular tachycardias were not related to pericardial biopsy procedure but caused by intrapericardial guidewire manipulation in patients with myopericardial disease.
In the study by Ziskind et al., 3 of 27 patients (3.7%) with advanced lung cancer died immediately after pericardial biopsy, but autopsy did not identify the cause of death. Additional complications included left apical pneumothorax (3.7%) and pericardial bleeding (7.4%). Mortality reported by Nugue et al. 9 was 2.1% and by Porte et al. 9 was 3.5%. Complications were associated with induction to anesthesia before pericardiocentesis in patients with large pericardial effusion. In contrast to surgical procedures, Endrys et al. 17 and Maisch et al. 2 reported no major complications. Minor complications included premature ventricular beats in 40% and a small subcutaneous hematoma in 4%. 16

Limitations of the Study
To calculate sensitivity of a diagnostic test, a referent value is necessary. However, the problem with the etiology of pericardial diseases is the lack of a single “gold standard.” Consequently, the final diagnosis is derived from several diagnostic methods. 8, 9 An additional problem is calculation of the pericardial biopsy specificity. Because the described methodology was applied only in patients with significant pericardial effusion, no true negative pericardial biopsies were expected.

This study summarizes our experience with pericardial biopsy and flexible pericardioscopy and was limited to histopathology of parietal biopsies. The number of patients included in the study was limited by the strict inclusion criteria. Diagnostic advantage of visceral pericardial (epicardial) biopsy was only demonstrated in a small, single-center series of patients, in whom immunohistochemistry, immunocytochemistry, and PCRs were applied. 2, 6 The present study would possibly benefit from application of these methods to prove viral or autoreactive pericarditis, as suggested by Maisch et al. 2 However, their diagnostic advantage against histology and especially the cost to benefit ratio remains to be proven. These analyses were therefore not applied in our study or any other published series of patients undergoing pericardial biopsy.

Implications of the Study
Nonsurgical pericardial biopsy has not yet been accepted in many major medical centers. Our results indicate superior diagnostic value of extensive pericardial sampling guided by pericardioscopy in large pericardial effusions of unknown etiology. These findings may warrant adoption of the procedure by tertiary cardiology institutions willing to develop the required facilities and staff and where large numbers of patients with pericardial disease are evaluated and treated.
Diagnostic Value of Pericardial Biopsy: Improvement With Extensive Sampling Enabled by Pericardioscopy
Petar M. Seferovic, Arsen D. Ristic, Ruzica Maksimovic, Vujadin Tatic, Miodrag Ostojic and Vladimir Kanjuh

_Circulation_. 2003;107:978-983; originally published online February 10, 2003;
doi: 10.1161/01.CIR.0000051366.97361.EA
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 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/107/7/978

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/