Improved Exercise Capacity and Differing Arterial and Venous Tolerance During Chronic Isosorbide Dinitrate Therapy for Congestive Heart Failure

CARL V. LEIER, M.D., PATRICIA HUSS, R.N., RAYMOND D. MAGORIEN, M.D., AND DONALD V. UNVERFERTH, M.D.

SUMMARY We studied 30 patients with moderate-to-severe congestive heart failure in a double-blind, randomized, placebo-controlled trial to determine the acute and long-term effects of isosorbide dinitrate on clinical status and on resting and exercise hemodynamics. Seventeen patients received placebo and 13 isosorbide dinitrate. First-dose isosorbide dinitrate (40 mg orally) decreased resting and exercise pulmonary capillary wedge pressure, pulmonic and systemic arterial pressures and pulmonic and systemic vascular resistances without augmenting exercise capacity. Compared with placebo, chronic therapy with isosorbide dinitrate (40 mg orally every 6 hours for 12 weeks) significantly improved clinical status and exercise capacity. Resting and exercise systemic blood pressure and systemic vascular resistance returned to baseline values during chronic isosorbide dinitrate therapy, but pulmonary capillary wedge pressure, pulmonary artery pressure and pulmonary vascular resistance remained improved. In patients with congestive heart failure, 12 weeks of oral isosorbide dinitrate therapy improves resting and exercise hemodynamics, exercise capacity, and clinical status; tolerance develops to the systemic arterial vascular effects without attenuation of the venous and pulmonary vascular effects.

ORAL isosorbide dinitrate, alone or combined with other vasodilators, is commonly administered to achieve additional preload reduction in congestive heart failure. First-dose isosorbide dinitrate (≥ 20 mg orally) favorably alters hemodynamics in congestive heart failure, but usually does not augment exercise capacity. Although the question of tolerance to chronic nitrate therapy remains controversial, Franciosa and colleagues have noted persistent improvement in resting hemodynamics and enhanced exercise capacity after chronic isosorbide dinitrate therapy in patients with congestive heart failure.

In this study, we examined and compared the effects of initial and chronic dosing of oral isosorbide dinitrate on resting and exercise hemodynamics and exercise capacity in patients with congestive heart failure. A double-blind, randomized, parallel, placebo-controlled design was used.

Methods

Patients

Thirty-nine patients with moderate-to-severe congestive heart failure were entered into the study. The patients were randomized by computer into two treatment groups: placebo (21 patients) and isosorbide dinitrate (18 patients). Four patients of the placebo group and five of the isosorbide dinitrate group were excluded from the study and subsequent analysis. The reasons for exclusion in the placebo group were noncompliance in two patients, frequent hospitalizations in one patient and sudden death in one patient. In the isosorbide dinitrate group, four patients were excluded because of sudden death and one because of noncompliance. One placebo patient died of ischemic cardiomyopathy 3 days after initiation of the study drug. In the isosorbide dinitrate group, three patients with ischemic cardiomyopathy died 12, 27, and 35 days after the onset of study; the fourth patient had severe idiopathic congestive cardiomyopathy and died on the forty-third day of the study.

The clinical and laboratory characteristics of the remaining 17 placebo patients and 13 isosorbide dinitrate patients are presented in table 1. There were no significant differences between the two groups in age, sex distribution, maximum duration of symptoms (dyspnea on exertion, paroxysmal nocturnal dyspnea, or pedal edema), functional classification (New York Heart Association), etiologic diagnosis, frontal heart area on chest roentgenogram, and the presence of atrial fibrillation or left bundle branch block. Diagnoses were established in all patients by right- and left-heart catheterization, left ventriculography, and coronary angiography within 2 months before the beginning of this study. Five of the placebo patients and four isosorbide dinitrate patients had mild-to-moderate mitral regurgitation.

Sixteen of the placebo patients were taking an oral digitalis preparation (one 0.375 mg/day, 12 0.25 mg/day, one 0.125 mg/day and two digoxin, 0.1 mg/day). Ten of the isosorbide dinitrate patients were taking oral digitalis (two 0.375 mg/day, seven 0.25 mg/day, and one 0.125 mg/day). The average daily dose of furosemide at the beginning of the study was 47 ± 30 mg (± sd) for the placebo group and 37 ± 26 mg for the isosorbide dinitrate group. The digitalis dosage was not altered during the study, but the furosemide dosage was adjusted based on symptoms, physical signs and body weight. During hemodynamic measurements, digitalis and diuretics were administered in the mid- to late afternoon to avoid the hemodynamic

From the Cardiology Division, Ohio State University College of Medicine, Columbus, Ohio.

Supported by the Central Ohio Heart Chapter of the American Heart Association and the James C. Castro Cardiovascular Research Fund. Dr. Magorien is an Investigator for the Central Ohio Heart Chapter of the American Heart Association.

Address for correspondence: Carl V. Leier, M.D., 653 Means Hall, 1655 Upham Drive, Columbus, Ohio 43210.

Received September 1, 1982; revision accepted December 17, 1982.

Circulation 67, No. 4, 1983.

817
TABLE 1. Clinical and Laboratory Features of the Patient Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Placebo</th>
<th>Isosorbide dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>47 ± 15</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Male/female</td>
<td>14:3</td>
<td>11:2</td>
</tr>
<tr>
<td>Duration of symptoms (months)*</td>
<td>15 ± 16</td>
<td>13 ± 17</td>
</tr>
<tr>
<td>NYHA functional class III/IV</td>
<td>13:4</td>
<td>10:3</td>
</tr>
<tr>
<td>Etiological diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Ischemic</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Post MVR</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Frontal heart area14 (% above predicted)*</td>
<td>50 ± 30%</td>
<td>45 ± 31%</td>
</tr>
<tr>
<td>Electrocardiographic evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>3†</td>
</tr>
<tr>
<td>Left BBB</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Mean ± SD.
†One patient also had a permanent-demand right ventricular pacemaker.

Abbreviations: BBB = bundle branch block; MVR = mitral valve replacement with prosthesis; NYHA = New York Heart Association.

effects of peak absorption. Starting 14 days before the study, no other vasodilator drugs were administered.

Protocol

Written, informed consent was obtained from each patient before the study. The invasive hemodynamic studies and bicycle ergometry were performed during hospitalization. The remaining studies and outpatient follow-up were carried out in the Heart Failure Research Laboratory of the Ohio State University Outpatient Clinic.

At baseline, all patients underwent complete history recording, physical examination, chest roentgenography, electrocardiography, M-mode echocardiography, measurement of systolic time intervals, and treadmill exercise testing. That evening, a flow-directed, triple-lumen thermodilution catheter was inserted percutaneously into a subclavian vein and positioned in the pulmonary artery. The next morning (postabsorptive state), supine resting, upright resting, and upright bicycle exercise hemodynamic studies were performed. The patients were randomized in double-blind fashion to placebo or isosorbide dinitrate. The placebo and isosorbide dinitrate tablets were identical in appearance. When the postexercise hemodynamic measurements returned to baseline, the first dose of placebo or isosorbide dinitrate, 40 mg, was administered orally. Sixty to 90 minutes later, supine resting, upright resting, and upright bicycle exercise hemodynamic studies were repeated.

The patients were discharged and took half-doses of the study drug for 2 weeks, and then advanced to the full dosage of 40 mg isosorbide dinitrate or comparable placebo tablets orally every 6 hours. The dosage had to be increased more gradually in one patient who had headaches, another who experienced near-syncope, and a third patient who had blurred vision at the maximal dosage; all three patients were in the isosorbide dinitrate group. Clinical evaluation by a physician, symptom survey, pill counts, and treadmill exercise testing were performed 1, 2, 4, 8, and 12 weeks after the beginning of the study. M-mode echocardiography and systolic time intervals were obtained at 4, 8, and 12 weeks. Treadmill and noninvasive testing were routinely performed 60–90 minutes after the dose. At 12 weeks, the patients were rehospitalized. A flow-directed, triple-lumen thermodilution catheter was introduced percutaneously and positioned in the pulmonary artery. The next morning, just before a dose (or 5–6 hours afterward), supine resting, upright resting and upright bicycle exercise hemodynamic studies were performed. These studies were repeated 60–90 minutes after a dose of the randomized treatment drug.

Procedures and Measurements

The noninvasive studies (M-mode echocardiography and systolic time intervals) were obtained on an Electronics for Medicine Echo IV unit as described previously.15,16 Echocardiographic determinants15,16 of left ventricular performance included percent change in the minor-axis dimension from diastole to systole (%ΔD) and velocity of circumferential fiber shortening (Vcf), and the systolic time intervals determinant was the ratio of the ejection period to left ventricular ejection time (PEP/LVET).17 Left ventricular dias-tolic volumes were measured by M-mode echocardiography and calculated using the formula reported by Pombo and colleagues.18

Two forms of exercise testing were used. Hemodynamic responses to exercise were determined during upright bicycle ergometry, which provides technical advantages over other forms of exercise in our laboratory. Outpatient treadmill exercise was used to evaluate the patient’s day-to-day outpatient activity and ambulatory tolerance.

Treadmill testing was performed on an Avionics Del Mar 599 treadmill interfaced with a Sanborn 760-6A Hewlett Packard Visoscope. The Bruce protocol19 modified to include an initial 180-second warm-up phase (0° at 1 mph) was used.

The indwelling pulmonary artery catheter, interfaced with Becton-Dickinson Electrodyne PR-18A pressure amplifiers and ST419 and WR4D recording systems, provided measurements of pulmonary artery pressure and pulmonary capillary wedge (arterial occlusive) pressure. For both supine and upright central pressure measurements, the pressure transducer was positioned at the intersection of the midaxillary line and a perpendicular line was drawn through the fourth intercostal space (parasternal). Thermodilution cardiac outputs were determined in triplicate (five measurements if the variation was more than 10%) with an Instrumentation Laboratories 601 computer and 602 recorder. Systemic blood pressure was measured by cuff and mercury column sphygmomanometer. Calcul-
lations included cardiac index (l/min/m²) = cardiac output/body surface area; stroke volume index (ml/beat/m²) = cardiac index × 1000/heart rate; systemic vascular resistance (dyn-sec-cm⁻²) = mean systemic blood pressure × 80/cardiac output; and pulmonary vascular resistance (dyn-sec-cm⁻²) = mean pulmonary artery pressure × 80/cardiac output.

Bicycle ergometry was performed on a Quinton Uniwork ergometer model 845. The work load was started at 50 kg-m/min; increased to 100 kg-m/min at 180 seconds and then increased by 100 kg-m/min every 180 seconds. Hemodynamic measurements were made before exercise, at 135–180 seconds of each work increment and at maximal exercise. All subjects completed the first 180 seconds of bicycle exercise; the hemodynamic measurements obtained at this level were therefore used as the standard submaximal exercise values. Maximal exercise duration for both bicycle ergometry and treadmill testing was the time at which excessive fatigue or dyspnea precluded continuation.

Statistical Analysis
Analysis of variance for repeated measures was used to determine if changes were significantly different from baseline values. Comparisons between treatment groups were made with one- and two-way analyses of variance. Changes in functional class and patient characteristics between groups were compared by chi-square analysis. A p value < 0.05 indicated a significant change. Values are given as mean ± SD.

Results

Clinical Course
During the 3-month study, four placebo patients improved one functional class (New York Heart Association), 12 remained unchanged and one patient deteriorated by one functional class. In the isosorbide dinitrate group, eight patients improved one functional class and five remained unchanged (p = 0.10 vs placebo). The mean body weight of both groups did not change significantly (81 ± 12 vs 82 ± 12 kg for placebo and 83 ± 22 vs 85 ± 23 kg for isosorbide dinitrate) during the study. The placebo group required an increase in the daily mean furosemide dose of 56 ± 80 mg (p < 0.05), compared with an increase of 25 ± 66 mg (p > 0.05) for the isosorbide dinitrate group.

Noninvasive Studies and Treadmill Exercise Testing
The results of echocardiographic and systolic time interval testing are presented in figure 1. The %ΔD and Vcf increased modestly but significantly, and end-diastolic volume decreased for the isosorbide dinitrate group compared with baseline values. These variables did not change significantly in the placebo group, and there were no differences between corresponding mean values of the two groups. The PEP/LVET did not change significantly in either group.

Exercise duration during outpatient treadmill testing increased significantly for the isosorbide dinitrate group at 30, 60 and 90 days (fig. 2). The mean value at 90 days was significantly greater than that of the placebo group.

Rest and Exercise Hemodynamic Studies
Table 2 presents the supine resting hemodynamic data. Placebo did not alter any hemodynamic variable 1 hour after acute dosage, 5–6 hours after a dose during the chronic phase (i.e., predose of chronic phase) or 1 hour after a dose during the chronic dosing phase. Initial-dose isosorbide dinitrate (40 mg orally) significantly decreased pulmonary capillary wedge pressure, mean pulmonary artery pressure, mean systemic blood

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Results of noninvasive testing. Fractional shortening (%ΔD), velocity of circumferential fiber shortening (Vcf), and end-diastolic volume (EDV) were obtained from M-mode echocardiography. The ratio of the prejection period to left ventricular ejection (PEP/LVET) was calculated from simultaneous recordings of carotid pulse, precordial phonocardiogram and a scalar ECG lead.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Exercise capacity determined from outpatient treadmill testing at specific intervals during the course of the study.
pressure and the pulmonary and systemic vascular resistance. Five to 6 hours after a dose during chronic isosorbide dinitrate dosing (predose of chronic phase), the pulmonary capillary wedge pressure, mean pulmonary artery pressure and pulmonary vascular resistance remained decreased below baseline and dropped further 1 hour after a dose. Systemic blood pressure and systemic vascular resistance returned to baseline during the chronic dosing phase for determinations before and 1 hour after a dose.

Hemodynamic data obtained during upright resting and upright bicycle exercise (submaximal and maximal) are presented in figures 3, 4 and 5. Isosorbide dinitrate effected the same directional changes of the same hemodynamic variables during upright rest as during supine rest (table 2). During submaximal and maximal exercise, initial-dose isosorbide dinitrate significantly decreased pulmonary capillary wedge pressure, mean pulmonary artery pressure, mean systemic blood pressure, and pulmonary and systemic vascular resistances below predose and corresponding placebo values (figs. 3 and 4). During the chronic dosing phase, systemic blood pressure and systemic vascular resistance at rest and exercise were no longer significantly affected by isosorbide dinitrate (fig. 4). Exercise pulmonary capillary wedge pressure, mean pulmonary artery pressure and pulmonary vascular resistance remained significantly below the corresponding placebo values 5–6 hours after a dose (the predose determination) of isosorbide dinitrate during chronic dosing (fig. 3). One hour after another isosorbide dinitrate dose, only the pulmonary capillary wedge pressure and the mean pulmonary arterial pressure at maximal exercise decreased significantly below the already reduced predose values. Neither placebo nor isosorbide dinitrate (initial dose or chronic dosage) altered exercise cardiac index, stroke volume index or heart rate significantly.

Initial-dose isosorbide dinitrate did not increase exercise duration (fig. 3). Chronic dosage (both before and 1 hour after a dose) with this drug increased exercise capacity above both placebo and initial values.

### Discussion

This double-blind, randomized, parallel, placebo-controlled study demonstrates that isosorbide dinitrate elicits beneficial clinical and hemodynamic effects in the setting of congestive heart failure. Acute isosorbide dinitrate improved resting and exercise hemodynamics by lowering the elevated pulmonary capillary wedge pressure, pulmonary artery pressure, and pulmonary and systemic vascular resistances. As noted by others,6,7 first-dose isosorbide dinitrate did not augment exercise capacity. Compared with chronic placebo therapy, chronic isosorbide dinitrate therapy caused a persistent reduction in resting and exercise pulmonary capillary wedge pressure and pulmonary artery pressure and pulmonary vascular resistance. Chronic isosorbide dinitrate therapy also increased exercise capacity and, compared with placebo, improved the clinical status as assessed by functional classification and diuretic requirements. It is noteworthy, but not statistically significant, that four patients (24%) of the isosorbide dinitrate group who were projected to complete the study died suddenly, compared with one of the placebo group (6%). We cannot explain this observation. The only apparent differences between the two groups were isosorbide dinitrate treatment and a higher, but statistically insignificant, prevalence of ischemic cardiomyopathy in the isosorbide dinitrate

---

**Table 2.** Supine Resting Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Initial phase</th>
<th>Chronic phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before dose</td>
<td>1 hour after dose</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>ISDN</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(systoles/min)</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>±17</td>
<td>±15</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.49</td>
<td>2.30</td>
</tr>
<tr>
<td>(l/min/m²)</td>
<td>±0.54</td>
<td>±0.85</td>
</tr>
<tr>
<td>Stroke vol index</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>(ml/beat/m²)</td>
<td>±9</td>
<td>±13</td>
</tr>
<tr>
<td>PCWP</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>±10</td>
<td>±9</td>
</tr>
<tr>
<td>Mean SBP</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>±15</td>
<td>±9</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>±13</td>
<td>±10</td>
</tr>
<tr>
<td>SVR</td>
<td>1583</td>
<td>1701</td>
</tr>
<tr>
<td>(dyn-sec-cm⁻⁵)</td>
<td>±529</td>
<td>±773</td>
</tr>
<tr>
<td>PVR</td>
<td>587</td>
<td>670</td>
</tr>
<tr>
<td>(dyn-sec-cm⁻⁵)</td>
<td>±232</td>
<td>±503</td>
</tr>
</tbody>
</table>

*p < 0.05 vs predose values.
†p < 0.05 vs placebo (n = 17).
‡p < 0.05, corresponding chronic vs initial phase data points.

Abbreviations: PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SBP = systemic blood pressure; SVR = systemic vascular resistance; P = placebo; ISDN = isosorbide dinitrate.
group (41%, seven of 17 patients vs 28%, five of 18 patients). However, neither nitrate therapy nor ischemic cardiomyopathy has been convincingly associated with a higher incidence of sudden death compared with placebo or other types of cardiomyopathy.

It is not clear why chronic isosorbide dinitrate therapy improved exercise tolerance. Chronic relief of elevated ventricular filling pressures, pulmonary artery pressure and pulmonary vascular resistance at rest, and particularly during exercise, is probably the most important factor. These favorable hemodynamic effects would tend to blunt the development of exercise-induced dyspnea, thereby allowing a greater exercise capacity for patients limited primarily by dyspnea. Quantitative analyses of activity records demonstrated that after the 2 weeks of treatment, the isosorbide dinitrate patients were significantly more active physically than the placebo group, which indicates that the chronic hemodynamic improvement was translated into increased physical activity and resulted in exercise-induced physical conditioning. Augmentation of treadmill and bicycle exercise capacity resulted. Franciosa et al.13 reported that chronic isosorbide dinitrate ther-
apy augmented exercise capacity without causing persistent hemodynamic improvement during exercise; however, the mean pulmonary capillary wedge pressure during exercise remained below control and may not have achieved a statistically significant change, based on the low number of patients (n = 8), and the pulmonary artery pressure and resistance data were not reported. A redistribution of nutritional blood flow to skeletal muscle (despite no change in resting and exercise cardiac output) or drug-induced physical conditioning cannot be excluded as possible contributory factors. However, the persistent improvement of resting and exercise hemodynamics with chronic nitrate therapy in our study and the documented increase in physical activity for the same group of patients obviates the necessity to invoke blood flow redistribution or drug-induced conditioning as primary explanations for the improvement of exercise capacity.

During chronic therapy, tolerance developed to the systemic arterial-arteriolar effects of isosorbide dinitrate, while the systemic venous and pulmonary vascular effects remained intact. The reasons for this different course of tolerance development with chronic dosing are not answered by this study. Preliminary data suggest that a systemic arterial-to-venous nitrate concentration gradient exists during nitrate administration.23 Systemic arteries, arterioles, or capillaries may therefore be sequestering a considerable amount of circulating nitrate. It is possible that during chronic moderate- or high-dose nitrate therapy, the systemic arteries and arterioles are exposed to a continually higher nitrate concentration relative to the venous vasculature. As a result, the systemic arteries and arterioles may undergo a form of selective downregulation or develop a biochemical-physiologic compensatory mechanism. Equally attractive explanations include differences (e.g., structure, affinity or regulation) in the venous and pulmonary vascular vs systemic arterial and arteriolar nitrate receptors and a greater susceptibility of the systemic arterial-arteriolar receptors to biochemical alteration (e.g., oxidation of critical sulf-hydryl groups).9 With the development of systemic arterial-arteriolar tolerance, the major long-term effects of isosorbide dinitrate reside in the systemic venous and pulmonary vascular systems. Tolerance to chronic isosorbide dinitrate therapy was not demonstrated in these systems; in fact, the values 5–6 hours after a dose during chronic administration were virtually identical in direction and magnitude of change to the first-dose responses (determined 1–1½ hours after dosing), indicating that the pharmacodynamic effects plateau with chronic isosorbide dinitrate dosing.

We conclude that chronic oral isosorbide dinitrate, 40 mg every 6 hours, provides sustained beneficial hemodynamic effects at rest and during exercise in patients with congestive heart failure. Despite its lack of effect on cardiac output and stroke volume, chronic isosorbide dinitrate improves exercise capacity and the clinical status of patients with heart failure. Oral isosorbide dinitrate, alone or combined with afterload-reducing agents, occupies an important role in the chronic medical management of congestive heart failure.

Acknowledgment

The authors thank Max Bacher, Karen Pacht, R.N., and Mitzi Prosser for their technical assistance. We thank Sam Song, M.D., Ph.D., Associate Medical Director of Ives Laboratories (New York) for generously supplying our laboratory with isosorbide dinitrate and placebo tablets.

References

17. Lewis HP, Leighton RF, Forester WF, Weisler AM: Systolic time intervals. In Noninvasive Cardiology, edited by Weisler AM. New York, Grune and Stratton, 1974, p 301
Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure.
C V Leier, P Huss, R D Magorien and D V Unverferth

*Circulation*. 1983;67:817-822
doi: 10.1161/01.CIR.67.4.817

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 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/67/4/817

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/