Intravenous Isosorbide Dinitrate in Patients with Refractory Pump Failure and Acute Myocardial Infarction

Babeth Rabinowitz, M.D., Israel Tamari, M.D., Ella Elazar, M.Sc., and Henry N. Neufeld, M.D.

SUMMARY We studied the hemodynamic effects of isosorbide dinitrate administered by continuous i.v. infusion to 22 patients with chronic refractory pump failure and 18 with pump failure due to acute myocardial infarction. In patients with severe pump failure, i.v. ISDN markedly decreased pulmonary capillary wedge pressure ($p < 0.001$), moderately increased cardiac output ($p < 0.01$), and decreased systemic vascular resistance (SVR) ($p < 0.001$). There were no deleterious effects on arterial pressure and heart rate. The effects obtained in acute and chronic left ventricular failure were similar. Patients with initial SVR levels lower than 1500 dyn-sec-cm$^{-1}$ did not significantly increase their cardiac output ($p < 0.005$). Cardiac output increased more than 25% only in patients with initial high SVR levels (> 2000 dyn-sec-cm$^{-1}$). Positive correlations were found between high SVR and elevated plasma catecholamines ($r = 0.53, p < 0.005$) and between the initial SVR and initial heart rate ($r = 0.70, p < 0.01$). The i.v. administration of isosorbide dinitrate appears to be an efficient therapy, particularly in selected patients with ischemic pump failure.

NITRATE PREPARATIONS and other vasodilators have been used to treat acute and chronic pump failure, but few data have been reported on the effects of i.v. isosorbide dinitrate (ISDN). Although nitrates are predominantly venodilators, decreases in systemic vascular resistance and increases in cardiac output have been reported. Nitrates are helpful in many patients with coronary heart disease, although a sudden, sharp decrease in the diastolic arterial pressure may enhance myocardial ischemia, particularly in the acute cases.

The present study was performed to evaluate the hemodynamic effects of i.v. ISDN in 40 patients with acute and chronic pump failure. Serial determinations of plasma catecholamines were also made to assess their relation to hemodynamic status and response to therapy.

Patients and Methods

Forty patients with pump failure received i.v. ISDN (Isoket) in a dose range of 2–8 mg/hour, based on the hemodynamic and clinical response. We studied 22 consecutive patients with chronic refractory pump failure (group A) and 18 patients with acute myocardial infarction and pump failure (group B) (table 1).

Refractory pump failure (group A) was manifest by persistent left-heart failure despite intensive conventional therapy. All patients in this category had dyspnea and hypoxia, wet rales and radiographic evidence of pulmonary venous congestion and cardiomegaly. Medical therapy in these patients included large i.v. doses of potent diuretics, digitalis, and bed rest in hospital. Other therapy included correction of electrolyte imbalance and treatment of arrhythmias.

The patients with chronic ischemic failure (group A, subgroup 1) all had recurrent myocardial infarction. These patients were not considered for surgery either because of their poor left ventricular function or because their coronary anatomy did not appear amenable to bypass grafting. Poor left ventricular function was demonstrated noninvasively or by complete cardiac catheterization and angiography. The left ventricular ejection fraction was less than 25% with diffuse hypokinesis and areas of akinesis or dyskinesis on nuclear ventriculography and, when measured, left ventricular end-diastolic pressure was greater than 20 mm Hg. Five of the coronary patients had significant mitral regurgitation and systolic regurgitant murmurs. Mitral regurgitation was diagnosed in three patients as 3+ on contrast ventriculography and was docu-
Table 1. Use of Intravenous Infusion of Isosorbide Dinitrate in 40 Patients

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A Chronic refractory pump failure</td>
<td>22</td>
</tr>
<tr>
<td>Subgroup A1 Coronary artery disease</td>
<td>15</td>
</tr>
<tr>
<td>Subgroup A2 Cardiomyopathy</td>
<td>4</td>
</tr>
<tr>
<td>Subgroup A3 Rheumatic valvular insufficiency</td>
<td>3</td>
</tr>
<tr>
<td>Group B Acute myocardial infarction with pump failure</td>
<td>18</td>
</tr>
</tbody>
</table>

...distributed by giant V waves on the pulmonary capillary wedge pressure tracing in two other patients not previously catheterized.20

The four patients with congestive cardiomyopathy (nonischemic) all had cardiomegaly by x-ray and echocardiography. A coronary cause was excluded by lack of suggestive clinical history, ECG or coronary arteriography that demonstrated normal coronary vessels.

In three patients, the underlying pathology was inactive rheumatic valvular heart disease. Two had severe mitral regurgitation and one severe aortic regurgitation. They were in refractory pump failure and received i.v. ISDN before surgery.

All patients with chronic refractory pump failure (group A) were therefore patients hospitalized because their clinical condition worsened and was increasingly refractory to therapy. No acute event occurred before the initiation of therapy with i.v. ISDN.

Group B included 18 patients studied during an acute myocardial infarction, defined by the presence of at least two of the following criteria: typical history, typical serial electrocardiographic changes, and characteristic elevations of CK and LDH isoenzymes.21 These patients also had left-heart failure unresponsive to diuretics and narcotics (table 1).

The average age was 60 years in group A (range 46–77 years), and 57 years in group B (range 41–70 years). Group A included 18 men and four women and group B 16 men and two women.

**Hemodynamic Measurements**

A triple-lumen, balloon-tipped Swan-Ganz thermomation catheter was introduced through an antecubital vein and passed into the pulmonary artery. Right atrial (RA), pulmonary arterial (PA) and pulmonary capillary wedge (PCWP) pressures were continuously monitored. Cardiac output (CO) was measured in triplicate by the thermodilution technique with a bedside computer (Instrumentation Laboratories). Arterial blood pressure (AP) was measured either directly by an intraarterial line or from repeated cuff readings. Mean AP was calculated as D + (S – D)/3, where S is the systolic pressure and D the diastolic pressure (mm Hg). Systemic vascular resistance (SVR) was calculated as 80 (AP – RA)/CO (dyn-sec-cm⁻²).

The hemodynamic criteria for entrance into the study were PCWP greater than 20 mm Hg and systolic AP greater than 90 mm Hg. During the study, diuretics, narcotics and oral nitrates were withheld. The patients taking digitalis continued their maintenance dose. Anticoagulants, antibiotics and lidocaine were continued or started as necessary.

ISDN in D5W was administered intravenously, starting at a dose of 2 mg/hour. In all patients, baseline hemodynamic measurements were obtained before the infusion at least twice during a minimum period of 30 minutes to ensure stable control levels; pressures were recorded 15 minutes, 30 minutes and 1 hour after the beginning of therapy. Later, pressures were measured every 2–3 hours, and cardiac output was measured at least twice every 24 hours. The dose was gradually increased to achieve a maximal decrease in PCWP, while maintaining a systolic AP of at least 90 mm Hg. The maximal dose administered was 8 mg/hour. The dose at which "optimal" values of PCWP, AP and CO were achieved in individual patients was maintained for at least 24 hours, and hemodynamic data were obtained at that dose level.

**Measurement of Catecholamines**

Total plasma catecholamines were determined fluorometrically using the method described by Renzini et al.,23 modified by Jiang,24 and used by us previously.25 The upper level of normal in our laboratory is 300 ng/l.

Fifteen of the 23 patients with chronic pump failure (subgroup A1) and seven of 18 patients with acute myocardial infarction (group B) had daily determinations of plasma catecholamines (between 8 a.m. and 2 p.m.). In subgroup A1, the blood samples were drawn 2–3 minutes after the hemodynamic measurements.

**Statistical Analysis**

Changes in the hemodynamic variables were analyzed by paired t test. The linear regressions of SVR and heart rate on catecholamines were estimated by the least-squares method. Estimates of correlation coefficients and changes during ISDN therapy that could not be different from zero due to sampling variation, with probability of 0.05 or larger, were denoted as significant.

**Results**

**Hemodynamic Profile**

**Group A**

The patients in chronic refractory heart failure (group A) had significant hemodynamic improvement during i.v. ISDN. In subgroup A1 (the 15 patients with ischemic pump failure), the following hemodynamic effects were observed (figs. 1A–1E).

The initial mean PCWP varied from 21–42 mm Hg. PCW decreased markedly in 12 of 15 patients. Changes in the whole group were highly significant (p < 0.001). CO increased moderately (p < 0.01). The mean AP decreased in patients who had a high initial AP, but was not affected in the other patients. The change in heart rate had a similar pattern to that of AP. The changes of both AP and heart rate in the whole group showed a slight decrease (p < 0.02). Cal-
SVR decreased in the whole group \( (p < 0.01) \). SVR decreased markedly in patients who had high initial values, but did not change in patients with an initially low SVR. Three patients had low-to-normal initial SVR (950, 1200 and 1450 dyn-sec-cm\(^{-5}\)). All of the others had increased initial SVR; one patient had an SVR of 1700 dyn-sec-cm\(^{-5}\) and eight patients had SVR levels greater than 2000 dyn-sec-cm\(^{-5}\).

Figure 2 shows the individual initial levels of SVR plotted against the percent change in CO induced by ISDN in the 15 patients who had chronic ischemic pump failure. All seven patients who had an increase in CO greater than 25% had an initial SVR greater than 2000 dyn-sec-cm\(^{-5}\). However, if the patients are divided arbitrarily into two groups based on initial calculated SVR decreased in the whole group \( (p < 0.01) \). SVR decreased markedly in patients who had high initial values, but did not change in patients with an initially low SVR. Three patients had low-to-normal initial SVR (950, 1200 and 1450 dyn-sec-cm\(^{-5}\)). All of the others had increased initial SVR; one patient had an SVR of 1700 dyn-sec-cm\(^{-5}\) and eight patients had SVR levels greater than 2000 dyn-sec-cm\(^{-5}\).

Figure 2 shows the individual initial levels of SVR plotted against the percent change in CO induced by ISDN in the 15 patients who had chronic ischemic pump failure. All seven patients who had an increase in CO greater than 25% had an initial SVR greater than 2000 dyn-sec-cm\(^{-5}\). However, if the patients are divided arbitrarily into two groups based on initial
SVR, the subgroup with low-to-normal initial SVR (mean 1200 dyn-sec-cm⁻⁵) has a poorer response to ISDN in terms of CO increase than did the subgroup with a high initial SVR (mean 2370 dyn-sec-cm⁻⁵) (p < 0.005). A less pronounced correlation (p < 0.02) was found when the decrease in PCW was compared with the initial levels of SVR.

Figure 3 illustrates the hemodynamic effects of ISDN in the patients with chronic refractory pump failure due to ischemia. Their left ventricular function curves shifted markedly to the left and slightly upward.

In group A1, the five patients with ischemic mitral regurgitation appeared to respond more markedly than the 10 patients with chronic ischemic failure who did not have mitral regurgitation (fig. 4). However, the changes in PCW and CO appeared more marked because the initial hemodynamic profile in these patients showed poorer baseline function compared with the other subgroups.

The patients with chronic refractory pump failure not due to ischemia had similar hemodynamic responses. Figure 4 illustrates the average shift in ventricular function in all 22 patients and in various subgroups according to cause. The changes in CO and PCWP were statistically significant in the patients with chronic pump failure (both p < 0.001). The four patients in whom pump failure was caused by cardiomyopathy (group A2) and the three patients with rheumatic valvular insufficiency (group A3) had a response similar to that of patients with ischemic pump failure.

**Group B**

The patients with acute myocardial infarction and pump failure benefited markedly from i.v. ISDN. The
FIGURE 5. Effects of isosorbide dinitrate (ISDN) on left ventricular function curves in acute myocardial infarction patients with pump failure (group B); mean and individual levels before (open symbols) and during ISDN (closed symbols) are shown. The decrease pulmonary capillary wedge pressure (PCW) and the increase in cardiac output (CO) are both statistically significant (p < 0.001).

Plasma Catecholamines
Twenty-two patients, 15 from group A1 and seven from group B, had serial determination of plasma catecholamines during the daytime (table 2).

The initial levels of peripheral plasma catecholamines varied in both groups. In the patients who had high basic levels of circulating catecholamines, the hemodynamic improvement was accompanied by a decreased level of plasma catecholamines.

Hemodynamics and Circulating Catecholamines
in Chronic Ischemic Pump Failure
Because the patients with a high initial SVR appeared to benefit more from the ISDN therapy, we compared simultaneous measurements of SVR with the levels of circulating catecholamines in patients with chronic ischemic failure (group A1) before the initiation of ISDN therapy. The initial levels of catecholamines correlated with the initial SVR values (r = 0.538, p < 0.05) (fig. 7). The initial heart rate and the levels of plasma catecholamines also correlated in group A1 (r = 0.702, p < 0.01) (fig. 8).

Clinical Results
Each patient who improved hemodynamically also improved clinically. Attempts to discontinue the ISDN infusion led to the reappearance of pulmonary congestion and worsening of the hemodynamics. Resumption of the drug was followed by a marked improvement. In 10 of 22 patients with chronic pump failure (group A), we gradually decreased the i.v. ISDN and replaced it with sublingual and oral ISDN. These 10 patients left the hospital much improved and were followed as outpatients. Five patients who did not improve during the study died in intractable pump failure during the same hospitalization. Five patients improved temporarily, but later required combined therapy with dopamine and vasodilators; only two survived. One of the latter was a patient with rheumatic mitral and aortic regurgitation who later underwent surgery. The remaining two patients, who had rheumatic valvular insufficiency, improved during i.v.

Table 2. Total Plasma Catecholamines

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ISDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1870</td>
<td>750</td>
</tr>
<tr>
<td>2</td>
<td>1670</td>
<td>448</td>
</tr>
<tr>
<td>3</td>
<td>265</td>
<td>170</td>
</tr>
<tr>
<td>4</td>
<td>168</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>1650</td>
<td>560</td>
</tr>
<tr>
<td>6</td>
<td>450</td>
<td>275</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>160</td>
</tr>
<tr>
<td>8</td>
<td>214</td>
<td>210</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>220</td>
</tr>
<tr>
<td>10</td>
<td>500</td>
<td>325</td>
</tr>
<tr>
<td>11</td>
<td>120</td>
<td>130</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>250</td>
</tr>
<tr>
<td>13</td>
<td>280</td>
<td>275</td>
</tr>
<tr>
<td>14</td>
<td>300</td>
<td>250</td>
</tr>
<tr>
<td>15</td>
<td>1420</td>
<td>140</td>
</tr>
<tr>
<td>Group B (acute)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>300</td>
<td>230</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>3</td>
<td>710</td>
<td>205</td>
</tr>
<tr>
<td>4</td>
<td>140</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>255</td>
<td>240</td>
</tr>
<tr>
<td>6</td>
<td>900</td>
<td>350</td>
</tr>
<tr>
<td>7</td>
<td>214</td>
<td>410</td>
</tr>
</tbody>
</table>

Values are ng/l.
Abbreviation: ISDN = isosorbide dinitrate.

FIGURE 6. Effects of isosorbide dinitrate (ISDN) on mean levels of pulmonary capillary wedge pressure (PCW) and cardiac output (CO) in patients with acute pump failure (group B; n = 18; ■ = control; □ = during ISDN) and in those with chronic pump failure (group A; n = 15; ● = control; ○ = during ISDN).
therapy and were sent to surgery while receiving i.v. ISDN. In 14 of 18 patients with acute myocardial infarction and pump failure (group B), we gradually discontinued i.v. ISDN after 2–5 days and replaced it with oral ISDN or with diuretics alone. These patients left the hospital without any signs or symptoms of heart failure. The four patients who did not improve during the ISDN infusion subsequently received combined therapy with i.v. hydralazine and dopamine; three died in cardiogenic shock and one survived and was discharged from hospital on hydralazine, diuretics, and digoxin.

**Discussion**

There have been few reports on the use of i.v. ISDN, and most of the data are from patients with acute infarction or unstable angina. We studied the hemodynamic effects of ISDN administered by i.v. infusion to 40 patients with severe pump failure and obtained the following data.

Intravenous ISDN not only markedly reduced filling pressures, but also tended to increase CO moderately (figs. 1A and 1B and 3–6). There were no sharp decreases in arterial pressure (fig. 1C), which could lead to further enhancement of ischemia. In severe pump failure due to acute myocardial infarction, the hemodynamic effects were similar to those due to chronic severe pump failure (figs. 5 and 6). Intravenous ISDN was useful in the presence of valvular insufficiency, including mitral regurgitation due to ischemia (fig. 4).

Vasodilators are generally classified as venodilators acting on preload, arteriolodilators acting on afterload, and mixed agents acting on both sides of the peripheral vascular tree; nitrates are in the first group of agents, which act only on capacitance vessels. However, several investigators agree that patients in severe distress who have a low initial CO and markedly increased filling pressure might respond differently. Our data and clinical impression confirm these conclusions.

Goldberg and colleagues pointed out that patients with an initially high SVR responded to ISDN by shifting the left ventricular function curve upward and to the left, an effect similar to that of nitroprusside. However, the patients studied by these authors had pump failure due to valvular insufficiency. Our data showed that i.v. ISDN also produced moderate increases in CO in patients with severe pump failure without valvular insufficiency.

Although the general hemodynamic effects of i.v. ISDN demonstrated a statistically significant improvement in chronic patients, some patients did not benefit (figs. 3 and 5) and, in a few, PCWP did not decrease.

Armstrong et al. observed that some patients with heart failure may respond to nitroglycerin only with a reduction in right atrial pressure without significant change in left ventricular filling pressures. According to their data, the lack of hemodynamic response to nitrate preparations in certain patients cannot be predicted from control hemodynamic variables, but can be anticipated by previous i.v. nitroglycerin infusion. However, Baligadoo et al. claim that the initial value of the SVR can predict the effect of the nitrate on CO. Our data agree with theirs.

The patients in whom CO increased significantly in response to i.v. ISDN were those who had a high initial SVR (fig. 2). Patients who had low-to-normal initial SVR levels appeared to be poor responders to therapy, in the acute patients as well as in the chronic group. It appears, therefore, that initial SVR levels might predict the subsequent response to therapy. However, to prove the role of SVR as a predictor, a larger homogenous population with pump failure should be studied.

There appears to be an advantage of i.v. ISDN over nonparenteral nitrates. The use of a continuous infusion permits a homogenous plasma level and avoids
sharp fluctuations by a sublingual or even oral preparation. Moreover, it seems logical to start i.v. therapy with the same agent intended for later nonparenteral administration in chronic patients.

In patients with ischemic heart disease, i.v. administration under continuous hemodynamic monitoring may be preferable. Although we do not have data to directly compare the use of i.v. ISDN with i.v. nitroglycerin, Bussman et al. showed that i.v. nitroglycerin tends to produce sharp decreases in AP. This reduction in AP might enhance preexisting ischemia. Further studies are needed to evaluate this potential difference between nitrate preparations, because only limited data are available. A randomized comparison of i.v. ISDN and i.v. nitroglycerin would be of interest.

The catecholamine measurements provided interesting correlations with the hemodynamic data. Armstrong and colleagues took into consideration variations in the levels of circulating catecholamines or of angiotensin that might alter the response of the peripheral circulation in failure. Our limited data showed a relationship between the initially high SVR and levels of circulating catecholamines in ischemic pump failure (fig. 7). Another interesting finding is the correlation between the initial heart rates and simultaneous levels of catecholamines in patients with chronic, refractory ischemic failure (fig. 8). A possible mechanism is that the initial increases in both heart rate and SVR are due to the release of large amounts of catecholamines; the increase in heart rate is a response to the low CO and is mediated through catecholamines. It would be of interest to study hyperkinetic acute myocardial infarction patients, a subgroup that includes patients without pump failure who have an exaggerated hypertensive-tachycardic response. Accumulation of additional metabolic data in larger groups of chronic and acute patients with different hemodynamic profiles is necessary to evaluate the significance of these measurements and the value of circulating catecholamines levels as predictors of therapeutic response.

Our data demonstrate favorable effects of i.v. ISDN in patients with severe failure manifested by increased filling pressures and elevated SVR. The use of i.v. ISDN might be preferable to the use of other i.v. vasodilators, particularly in patients with ischemic pump failure.

Acknowledgment

The authors are indebted to Uri Goldbourt for the statistical analysis, the residents and nurses of the intensive coronary care unit who conscientiously supervised these patients, and to R. Klein, M.Sc., for technical help in the biochemical work. Isosorbide dinitrate (Isoket) was supplied by Pharma-Schwarz GmbH, Monheim, West Germany.

References

2. Kovick RB, Tiliisch JH, Berens SC, Bramowitz AD, Shine KI: Vasodilator therapy for chronic left ventricular failure. Circula-
24. Jiang NS, Stoffler SS, Piler GM, Wadel O, Sheps SG: Laboratory and clinical observations with a two-column cate-
Pathophysiology of Chest Pain in Patients with Cardiomyopathies and Normal Coronary Arteries

ANDRÉ PASTERNAC, M.D., JACQUES NOBLE, M.D., YVES STREULENS, M.D., ROBERT ELIE, M.D., PH.D., CLAUDIA HENSCHEL, M.D., PH.D., AND MARTIAL G. BOURASSA, M.D.

SUMMARY To clarify the pathogenesis of chest pain in patients with cardiomyopathies, we compared coronary blood flow and other indicators of ischemia at rest and during pacing-induced tachycardia in nine patients with cardiomyopathy (four hypertrophic and five congestive) and in five control subjects. Coronary blood flow was reduced at rest and during pacing in cardiomyopathy patients compared with controls. In patients with hypertrophic cardiomyopathy, pacing induced chest pain in all, increased ST-segment depression in three patients and increased coronary venous lactate concentration. With pacing, two of five patients with congestive cardiomyopathy had chest discomfort and three had increased ST-segment depression, but coronary venous lactate concentration did not change significantly. In both groups of cardiomyopathies, the ratio of the systolic and diastolic pressure-time indexes tended to decrease more than in controls during pacing. Thus, myocardial perfusion is decreased in patients with cardiomyopathy, both at rest and during pacing. The changes detected during pacing point to subendocardial ischemia as the likely mechanism for angina in hypertrophic and possibly also in congestive cardiomyopathy.

CHEST PAIN is a frequent symptom in patients with cardiomyopathy: 39–72% of patients with idiopathic hypertrophic cardiomyopathy experience anginal pain, and as many as 52% of patients with congestive cardiomyopathy report vague chest pain, despite the presence of normal or even dilated coronary arteries.

However, although myocardial blood flow per unit mass has already been studied in such patients, the pathophysiology of chest pain and its relationship to the usual markers of ischemia are not clear. Therefore, we measured myocardial perfusion at rest and during pacing in patients with hypertrophic and congestive cardiomyopathy and compared clinical and biochemical indicators of ischemia both at rest and during pacing in hypertrophic and congestive cardiomyopathies and in a control group.

Methods

Patient Selection

We reviewed the echocardiographic and hemodynamic data of all patients in whom cardiomyopathies were diagnosed during 1 year at the Montreal...
Intravenous isosorbide dinitrate in patients with refractory pump failure and acute myocardial infarction.
B Rabinowitz, I Tamari, E Elazar and H N Neufeld

Circulation. 1982;65:771-778
doi: 10.1161/01.CIR.65.4.771
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 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/65/4/771

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/