Immunomodulating Therapy With Intravenous Immunoglobulin in Patients With Chronic Heart Failure

Lars Gullestad, MD, PhD; Halfdan Aass, MD, PhD; Jan G. Fjeld, MD, PhD; Lisbeth Wikeby, RN; Arne K. Andreassen, MD, PhD; Halfdan Ihlen, MD, PhD; Svein Simonsen, MD, PhD; John Kjekshus, MD, PhD; Sigurd Nitter-Hauge, MD, PhD; Thor Ueland, BS; Egil Lien, PhD; Stig S. Frøland, MD, PhD; Pål Aukrust, MD, PhD

Background—Congestive heart failure (CHF) is characterized by enhanced immune activation, and immune-mediated mechanisms may play a pathogenic role in this disorder. Based on the immunomodulatory effects of intravenous immunoglobulin (IVIG), we hypothesized that IVIG could downregulate inflammatory responses in CHF patients and have potential beneficial effects on the left ventricular ejection fraction (LVEF).

Methods and Results—Forty patients with chronic symptomatic CHF and LVEF of <40%, stratified according to cause (ie, ischemic and idiopathic dilated cardiomyopathy), were randomized in a double-blind fashion to receive therapy with IVIG or placebo for a total period of 26 weeks. Our main findings were that (1) IVIG, but not placebo, induced a marked rise in plasma levels of the anti-inflammatory mediators interleukin (IL)-10, IL-1 receptor antagonist, and soluble tumor necrosis factor receptors; (2) significantly correlated with these anti-inflammatory effects, IVIG, but not placebo, induced a significant increase in LVEF from 26±2% to 31±3% (P<0.01), and this was found independent of the cause of heart failure; and (3) N-terminal pro–atrial natriuretic peptide decreased significantly after induction therapy and continued to decrease toward the end of study during IVIG therapy (P<0.001) but remained unchanged during placebo.

Conclusions—We demonstrated an IVIG-induced change in the balance between inflammatory and anti-inflammatory cytokines that favored an anti-inflammatory net effect in CHF. This effect was significantly correlated with an improvement in LVEF, suggesting a potential for immunomodulating therapy in addition to optimal conventional cardiovascular treatment regimens in CHF patients. (Circulation. 2001;103:220-225.)

Key Words: heart failure ■ inflammation ■ interleukins ■ immune system

Several studies have demonstrated that patients with congestive heart failure (CHF) are characterized by a sustained immune activation. This is reflected in increased circulating levels of inflammatory cytokines (eg, tumor necrosis factor [TNF]-α, interleukin [IL]-1)1–3 and enhanced expression of various inflammatory mediators within the failing myocardium (eg, adhesion molecules and TNF-α),1,4 independent of the cause of CHF.4

Increasing evidence suggests that inflammatory mediators (eg, TNF-α -and IL-1) may not only be markers of immune activation but may also induce myocardial dysfunction via various mechanisms, such as the regulation of apoptosis and impaired β-adrenergic responsiveness.5–7 Notably, the infusion of TNF-α in concentrations comparable to the circulating levels in CHF may promote left ventricular dysfunction in rats.8

Therapy with intravenous immunoglobulin (IVIG) has been tried in a wide range of immune-mediated disorders, such as Kawasaki’s syndrome, dermatomyositis, and multiple sclerosis.9,10 One non–placebo-controlled study has also suggested a beneficial effect of IVIG in acute cardiomyopathy.11 Several modes of action may be of importance for the clinical effects of IVIG in inflammatory disorders (eg, neutralization of microbial antigens and autoantibodies, Fc-receptor blockade, and complement inactivation).9,12,13 Moreover, we and others have demonstrated that IVIG may also influence the level of several cytokines and cytokine modulators, resulting in the downregulation of inflammatory responses.14,15

On the basis of the immunomodulatory effects of IVIG, we examined in the present pilot study whether IVIG could downregulate inflammatory responses in CHF patients. We also examined whether any potential modulation of the cytokine network after IVIG therapy was associated with any changes in left ventricular ejection fraction (LVEF). Patients with chronic CHF, due to either ischemic or idiopathic dilated cardiomyopa-
by guest on August 20, 2017 http://circ.ahajournals.org/ Downloaded from

A total of 5 months. Such dose schedules of IVIG have been widely
accepted as induction therapy (1 daily infusion at
the manufacturer’s instruction as induction therapy (1 daily infusion at
40% (3) had no changes in medication during the past 3 months,
and (4) were receiving optimal medical treatment and considered
unsuitable for surgical intervention. Patients were not included if
they had (1) evidence of myocardial infarction or unstable angina
during the past 6 months or (2) significant concomitant diseases such
as infections, pulmonary disorders, or connective tissue disease.
None of the patients changed the conventional cardiovascular treat-
ments during the study.

The cause of CHF was classified as coronary artery disease (CAD,
(n=23) or IDCM (n=9) on the basis of disease history and coronary
angiographic examination. The regional ethical committee approved the
study, and signed informed consent was obtained from each patient.

Methods

Patients

Forty patients with chronic stable CHF for >6 months were included
in the study (Table 1). The patients were included if they (1) were
classified in NYHA functional class II/III, (2) had an LVEF of
<40%, (3) had no changes in medication during the past 3 months,
and (4) were receiving optimal medical treatment and considered
unsuitable for surgical intervention. Patients were not included if
they had (1) evidence of myocardial infarction or unstable angina
during the past 6 months or (2) significant concomitant diseases such
as infections, pulmonary disorders, or connective tissue disease.
None of the patients changed the conventional cardiovascular treat-
ment regimen during the study.

The cause of CHF was classified as coronary artery disease (CAD,
(n=23) or IDCM (n=17) on the basis of disease history and coronary
angiographic examination. The regional ethical committee approved the
study, and signed informed consent was obtained from each patient.

IVIG Preparation

Octagam (Octapharma), which was produced from fresh frozen plasma
collected from Norwegian blood banks,15 is dispensed in sterile water
for infusion (Octapharma). Octagam is a whole blood plasma product,
which was produced from fresh frozen plasma from blood donors.
It is a high-purity plasma fraction with a low total protein content
and a high concentration of immunoglobulins. The product contains
some low-concentration cytokine network after IVIG therapy was associated with any
changes in cytokines. We primarily wanted to examine whether any potential modulation of the
cytokine network after IVIG therapy was associated with any
changes in cytokines and hemodynamic variables, of which LVEF was
considered to be the most important.

Test Protocol

At baseline and at the end of the study, the following tests were performed: (1) immunological variables (see later) and (2) LVEF,
assessed with ECG-synchronized gated radionuclide ventriculogra-
phy at rest. Autologous erythrocytes were labeled with 800 MBq
99mTc-pertechnetate according to a combined in vivo/in vitro tech-
nique as previously described.17 One physician performed all LVEF
measurements in a blinded fashion. At our laboratory, the standard
development of this method was found to be 2.1 EF%, giving a
coefficient of variation of 6% for LVEF values close to 30 EF%.17
Right ventricular ejection fraction (RVEF) was determined accord-
ing to the same method, as described earlier. (3) Hemodynamic
variables were assessed with right-sided heart catheterization. (4)
Exercise testing was performed with an electrically braked bicycle
ergometer. The test protocol consisted of a starting work rate of 20
W increasing by 20 W every other minute until exhaustion (defined
as an inability to keep the pedaling rate steady at 60 rpm). Oxygen
uptake (VO2) was measured with the EOS/SPRINT system. Peak VO2
was taken as the highest VO2 value observed. (5) Clinical evaluation
was assessed on the basis of NYHA classification as determined by
a cardiologist, and the McMaster Overall Treatment Evaluation
questionnaire was used to assess quality of life. (6) Plasma levels of
N-terminal pro–atrial natriuretic peptide (NT-pro-ANP) were mea-
sured (see later).

Blood Sampling Protocol

Blood samples were collected into pyrogen-free EDTA tubes during
right-sided heart catheterization from the pulmonary artery (mixed
venous blood). The tubes were immediately immersed in melting ice
and centrifuged within 15 minutes at 1000 rpm for 15 minutes, and plasma
was stored at −80°C until analysis. Samples were thawed only once.

Laboratory Analyses

TNF-α and IL-10 were measured with ELAs (Biosource Internationale).
StNFs p55 and p75 were analyzed with ELAs as described previously.
16 IL-1Ra and IL-1β were examined with ELAs, obtained from R&D
Systems. Nt-pro-ANP was measured with radioimmunoassay. The
coefficients of variation were <10% for all assays.

Statistical Analyses

Differences between groups were compared with Student’s t test or
Mann-Whitney U rank sum test for unpaired data. The Wilcoxon
g signed rank test was used for paired data. When analyzing variables
from >2 time points (ie, Nt-pro-ANP), repeated measures ANOVA
was used. For comparison of proportions, the χ2 test was used.
Relatives between variables were tested using Spearman’s rank
correlation test. The results are given as mean ± SEM, whereas the
changes in variables after treatment are expressed as mean values
with associated 95% CI if not otherwise stated. The probability
values are 2-sided and taken as significant at <0.05.

Results

Key demographic and hemodynamic parameters were similar in the
2 treatment groups (Table 1). Moreover, at baseline
there were no significant differences in the levels of cytokines

TABLE 1. Clinical Characteristics of the CHF Patients Who Participated in the Study

<table>
<thead>
<tr>
<th></th>
<th>IVIG (n=20)</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±1.3</td>
<td>61±2.0</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>18/2</td>
<td>15/5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±0.8</td>
<td>26.1±0.8</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>11 (55%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>IDCM</td>
<td>9 (45%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Duration of heart failure, y</td>
<td>3.7±0.5</td>
<td>3.4±0.4</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>19 (95)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Angiotensin II blockers</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17 (85)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>17 (85)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>7 (35)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM.
TABLE 2. Plasma Levels of Cytokines and Their Endogenous Modulators in 39 CHF Patients Before and After 6 Months of Treatment With IVIG or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mo</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo</th>
<th>Change</th>
<th>Differences in Changes Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVIG (n=19)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>22.1±2.0</td>
<td>19.2±1.8</td>
<td>−2.9 (−7.4 to 1.7)</td>
<td>26.6±3.0</td>
<td>28.7±4.1</td>
<td>1.5 (−1.7 to 4.6)</td>
<td>0.140</td>
</tr>
<tr>
<td>p55-TNFα, ng/mL</td>
<td>1.50±0.09</td>
<td>1.73±0.11</td>
<td>0.22 (0.13 to 0.32)†</td>
<td>1.66±0.12</td>
<td>1.62±0.10</td>
<td>−0.04 (−0.17 to 0.10)</td>
<td>0.006</td>
</tr>
<tr>
<td>p75-TNFα, ng/mL</td>
<td>1.62±0.12</td>
<td>2.69±0.26</td>
<td>1.06 (0.62 to 1.51)†</td>
<td>1.97±0.18</td>
<td>1.82±0.15</td>
<td>−0.15 (−0.39 to 0.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α/sTNFRs ratio</td>
<td>625±69</td>
<td>396±45</td>
<td>−229 (−364 to −93)†</td>
<td>665±93</td>
<td>741±131</td>
<td>60 (−30 to 150)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-1α, pg/mL</td>
<td>3.1±0.2</td>
<td>2.7±0.3</td>
<td>−0.4 (−0.9 to 0.1)</td>
<td>2.8±0.3</td>
<td>3.1±0.4</td>
<td>0.4 (0.1 to 0.6)*</td>
<td>0.030</td>
</tr>
<tr>
<td>IL-1Ra, pg/mL</td>
<td>324±20</td>
<td>509±53</td>
<td>186 (84 to 288)‡</td>
<td>318±20</td>
<td>294±18</td>
<td>−24 (−54 to 6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-1β/IL-1Ra ratio</td>
<td>7.9±0.7</td>
<td>4.9±0.7</td>
<td>−3.0 (−4.7 to −1.4)†</td>
<td>7.2±0.9</td>
<td>9.2±1.4</td>
<td>2.0 (0.4 to 3.6)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>3.1±0.2</td>
<td>5.1±0.5</td>
<td>2.0 (1.3 to 2.8)‡</td>
<td>2.8±0.2</td>
<td>2.5±0.1</td>
<td>−0.3 (−0.6 to 0.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM at baseline and 6 mo. Changes are given as mean and 95% CI in parentheses. TNF-α/sTNFRs ratio is defined as [TNF-α (trimer) (pmol/L)/(p55+p75-TNFα) (pmol/L)]×100. IL-1β/IL-1Ra ratio is defined as IL-1β (pmol/L)/IL-1Ra (pmol/L).

*P<0.05, †P<0.01, ‡P<0.001 vs baseline.

Between the placebo and the IVIG groups (Table 2). One patient in the IVIG group was withdrawn by a local physician 3 weeks after baseline due to paroxysmal atrial fibrillation.

Immunological Parameters

IL-1β increased significantly in the placebo, but not in the IVIG, group (Table 2). Simultaneously, IVIG, but not placebo, induced a marked increase in IL-1Ra levels (~57%), accompanied by a marked increase in IL-10 levels (~65%) (Table 2). Finally, although TNF-α tended to decrease after IVIG and increase after placebo treatment, IVIG, but not placebo, induced a rise in soluble p55-TNFα (~15%) and, in particular, soluble p75-TNFα (~65%) (Table 2). Thus, it appears that IVIG had a profound anti-inflammatory effect in CHF patients as reflected in enhanced levels of IL-10, IL-1Ra, and sTNFRs, as well as decreased levels of IL-1β/IL-1Ra and TNF-α/sTNFRs ratios. In contrast, no or even opposite changes were seen after placebo treatment, resulting in significant differences between the 2 groups for several of these parameters (Table 2).

Ventricular Function

LVEF increased significantly by 5 EF units after IVIG, whereas no significant change was seen in the placebo group (Figure 1, Table 3). Moreover, of the 19 CHF patients who received IVIG, 14 demonstrated an increase in LVEF, and 10 of these improved by >5 EF units. In contrast, only 4 of the patients in the placebo group showed a comparable improvement in LVEF (>5 U) (P<0.05 vs IVIG). No beneficial effect of IVIG was seen in the 4 patients with the lowest LVEF (~15% at baseline, Figure 1). We found no significant correlation between duration of heart failure and either LVEF at baseline or changes in LVEF after IVIG therapy. However, 3 of the 4 patients with no beneficial effect of IVIG had a markedly longer duration of heart failure symptoms (25, 10, and 6 years) compared with the other IVIG-treated patients (median duration of symptoms 2.5 years). The effect of IVIG on LVEF was independent of the cause of heart failure, increasing from 25±3% to 30±4% (P<0.05) in the CAD group and from 26±6% to 31±4% (P<0.05) in the IDCM group, with no changes during placebo in either of these groups. RVEF also improved after IVIG (~6 EF units, P<0.05), with no significant change in the placebo group (Table 3). However, RVEF is difficult to measure accurately, and caution is necessary when interpreting these results.

Notably, in the IVIG, but not in the placebo, group, there was a strong positive correlation between the changes in IL-1Ra, IL-10, and both types of sTNFRs and the change in LVEF (Figure 2). In contrast, the change in IL-1β was negatively correlated with the change in LVEF in both the IVIG and placebo groups (Figure 2).

Other Clinical and Hemodynamic Variables

After IVIG, but not after placebo, treatment, hemodynamic variables obtained during right-sided heart catheterization showed a modest but significant decrease in pulmonary capillary wedge pressure and pulmonary artery pressure (Table 3). Moreover, after IVIG therapy, exercise capacity as assessed by peak VO2 increased by ~6% and peak workload increased by ~10%, whereas no changes were observed in the placebo group (Table 3). Regarding the peak workload,

Figure 1. LVEF as assessed by ECG-synchronized gated radionuclide ventriculography at rest in 39 CHF patients before and after 6 months of treatment with IVIG (n=19) or placebo (n=20). Mean±SEM values are given. In patients with particularly low LVEF at baseline (~15%), there was no increase in LVEF during IVIG therapy.
there was a significant difference in changes between IVIG and placebo treatment (Table 3). Functional status as assessed by NYHA class improved in the placebo and, in particular, the IVIG group (Table 3). In addition, in a quality-of-life questionnaire, the global estimate of changes demonstrated improvement in both the placebo (40% of patients) and, in particular, the IVIG group (73% of patients).

**Nt-pro-ANP**

Plasma levels of Nt-pro-ANP, which have been found to correlate with pulmonary artery pressures in CHF and thereby provide important prognostic information for CHF patients, decreased significantly after the induction therapy and continued to decrease toward the end of the study during IVIG therapy (Figure 3). No significant change was observed in the placebo group, resulting in a significant difference between the 2 groups (Table 3, Figure 3).

**Side Effects and Laboratory Status**

Eight subjects (2 with placebo and 6 with IVIG) had mild discomfort (chills or headache) during the first hours after infusion, 3 patients (all with IVIG) had a rise in temperature ($\geq 39.0^\circ$ C) immediately after infusion that persisted for a few hours, and 3 patients (all with IVIG) developed a mild itching rash after infusion that persisted for a few days. None of the patients had to withdraw from the study because of side effects. Blood was collected every month, but no changes in routine hematological parameters, serum creatinine, ASAT,
endothelial cells,12,13,20 and all of these factors may be involved in the pathogenesis of heart failure. Moreover, autoantibodies directed against β1-adrenoceptors may play a pathogenic role in CHF,31 and anti-idiotypic antibodies in the IVIG preparation may potentially neutralize such antibodies. Also, IVIG has been shown to modulate the release of cytokines in phagocytes through interaction with Fc-receptors on these cells,22 and we and others have shown that IVIG preparations may markedly enhance the release of IL-1Ra and sTNFRs from monocytes in vitro.12,23 Regardless of the mechanisms, our findings that demonstrate a marked anti-inflammatory outcome of IVIG on the cytokine network in CHF patients, significantly correlated with improvement of LVEF, suggest that this capacity to modulate the cytokine network may be of importance for the potential beneficial effect of IVIG in CHF. IL-10, IL-1Ra, and sTNFRs all have anti-inflammatory effects with potential relevance for the pathogenesis of CHF.3 IL-10 was recently found to enhance the release of IL-1Ra and sTNFRs from monocytes in vitro,12,23 and others have shown that IVIG preparations may markedly enhance the release of IL-1Ra and sTNFRs from monocytes in vitro.12,23 Both IL-1 and TNF-α can impair myocardial performance.5–7

### Discussion

The novel and important finding of the present study was a marked IVIG-induced change in the balance between inflammatory and anti-inflammatory mediators in CHF patients, favoring an anti-inflammatory net effect. This effect was significantly correlated with an improvement in LVEF. Several studies suggest that inflammatory cytokines are involved in the pathogenesis of CHF.1,2 However, most data that support the “cytokine hypothesis” are obtained through studies in animal models, in vitro experiments, and cross-sectional studies on cytokine levels in humans. It has also been reported that 1 dose of soluble p75-TNFR showed beneficial effect in a small population of CHF patients,18 that 1 bolus injection of IVIG improved LVEF in new-onset cardiomyopathy in a non–placebo-controlled study,11 and that the immunomodulating agent pentoxifylline enhanced LVEF in a placebo-controlled trial in patients with IDC.19 However, the present double-blind, placebo-controlled study shows for the first time that immunomodulation with IVIG has the potential to improve LVEF in CHF patients on optimal conventional cardiovascular treatment regimens. Our findings add further support to the notion that inflammatory mediators are involved in the pathogenesis of heart failure and suggest a potential for immunomodulating therapy in CHF.

A major finding in the present study was the marked rise in IL-10, IL-1Ra, and sTNFRs levels after IVIG treatment in CHF patients, resulting in a combined enhancement of several anti-inflammatory mediators. Several non–mutually exclusive modes of action may explain the beneficial effect of IVIG in immune-mediated disorders, and some of these may well be operative in CHF. Thus, IVIG has been found to induce complement inactivation, impair apoptosis, and inhibit leukocyte adhesion to endothelial cells,12,13,20 and all of these factors may be involved in the pathogenesis of heart failure. Moreover, autoantibodies directed against β1-adrenoceptors may play a pathogenic role in CHF,31 and anti-idiotypic antibodies in the IVIG preparation may potentially neutralize such antibodies. Also, IVIG has been shown to modulate the release of cytokines in phagocytes through interaction with Fc-receptors on these cells,22 and we and others have shown that IVIG preparations may markedly enhance the release of IL-1Ra and sTNFRs from monocytes in vitro.12,23 Regardless of the mechanisms, our findings that demonstrate a marked anti-inflammatory outcome of IVIG on the cytokine network in CHF patients, significantly correlated with improvement of LVEF, suggest that this capacity to modulate the cytokine network may be of importance for the potential beneficial effect of IVIG in CHF. IL-10, IL-1Ra, and sTNFRs all have anti-inflammatory effects with potential relevance for the pathogenesis of CHF.3 IL-10 was recently found to have protective effects on the development of atherosclerosis.24

![Figure 3. Plasma levels of Nt-pro-ANP, given as percentage change from baseline, in 39 CHF patients before and at different time points after initiation of treatment with IVIG (n=19) or placebo (n=20). Data are given as mean±SEM. *P<0.05, **P<0.01, and ***P<0.001 vs baseline. #P<0.05 for comparison of differences in changes between IVIG and placebo groups.](image-url)
Infections with certain microbes have recently been sug-

in both idiopathic dilated and ischemic cardiomyopathy. However, we found improved LVEF with IVIG were small at best. These preliminary observations on the “infectious hypothesis,” and several other factors that operate in ischemic heart disease, such as enhanced oxidative and fluid shear stress and oxidized LDL may all induce inflammatory responses within the myocardium. Based on the possible involvement of autoimmunity- or virus-induced mechanisms, previous studies of IVIG in heart disease have focused on myocarditis and acute cardiomyop-


Bozkurt B, Kribbs SB, Clubb FJ Jr, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-α promote progressive dys-


Libby P, Egan D, Skarlatos S. Roles of infectious agents in athero-


Acknowledgments

We thank Rita Skårdal, Anne Brunsvig, and Bodil Lunden for excellent technical assistance. This study was supported by the Research Council of Norway, the Norwegian Council of Cardiovas-

cular Disease, Anders Jahre’s Foundation, Octapharma, Hurdal, Norway, and Medinnova Foundation.

References


8. Bozkurt B, Kribbs SB, Clubb FJ Jr, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-α promote progressive dys-


Immunomodulating Therapy With Intravenous Immunoglobulin in Patients With Chronic Heart Failure


_Circulation_. 2001;103:220-225
doi: 10.1161/01.CIR.103.2.220

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 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/103/2/220

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/