Nonselective Versus Selective $\beta$-Adrenergic Receptor Blockade in Congestive Heart Failure
Differential Effects on Sympathetic Activity

Eduardo R. Azevedo, MD; Toshihiko Kubo, MD; Susanna Mak, MD; Abdul Al-Hesayen, MD; Anne Schofield, RN; Rebecca Allan, RN; Susan Kelly, RN; Gary E. Newton, MD; John S. Floras, MD, DPhil; John D. Parker, MD

Background—Activation of the sympathetic nervous system has important prognostic implications in chronic heart failure. Nonselective versus selective $\beta$-adrenergic receptor antagonists may have differential effects on norepinephrine release from nerve terminals mediated by presynaptic $\beta_2$-adrenergic receptors.

Methods and Results—Thirty-six patients with chronic heart failure were randomized to the nonselective $\beta$-blocker carvedilol or the selective $\beta$-blocker metoprolol (double-blind). Measurements of hemodynamics and cardiac and systemic norepinephrine spillover as well as microneurographic recordings of muscle sympathetic nerve traffic were made before and after 4 months of therapy. In the carvedilol group ($n=17$), there were significant reductions in both total body ($-1.7\pm0.5$ nmol/min, $P<0.01$) and cardiac norepinephrine spillover ($-87\pm29$ pmol/min, $P<0.01$). By contrast, in the metoprolol group ($n=14$), there were no significant changes in total body or cardiac norepinephrine spillover. Responses in the carvedilol group were significantly different from those observed in the metoprolol group ($P<0.05$). Both agents caused a reduction in heart rate and increases in pulse pressure, although mean arterial pressure did not change. Importantly, microneurographic measures of sympathetic nerve traffic to skeletal muscle did not change in either group.

Conclusions—Therapy with carvedilol caused significant decreases in systemic and cardiac norepinephrine spillover, an indirect measure of norepinephrine release. Such changes were not observed in patients treated with metoprolol. There was no effect of either agent on sympathetic efferent neuronal discharge to skeletal muscle. These findings suggest that carvedilol, a nonselective $\beta$-blocker, caused its sympathoinhibitory effect by blocking peripheral, presynaptic $\beta$-adrenergic receptors. (Circulation. 2001;104:2194-2199.)

Key Words: heart failure ■ receptors, adrenergic, beta ■ nervous system, autonomic ■ norepinephrine

The beneficial effect of $\beta$-blockers in the treatment of patients with chronic congestive heart failure (CHF) has now been demonstrated. Several $\beta$-blockers, including metoprolol, bisoprolol, and carvedilol, improve clinical outcome in CHF compared with placebo.1-3 To date, few trials have compared the relative efficacy of these agents. The fact that there may be clinically relevant differences between $\beta$-blockers has recently been highlighted by the BEST study, in which bucindolol, compared with placebo, failed to show a clear beneficial effect on mortality.4

There have been a few reports comparing metoprolol with carvedilol in patients with chronic CHF. Two studies reported no important differences in the effect of these drugs on symptoms, exercise capacity, or left ventricular function.5,6 Another larger, randomized study demonstrated that carvedilol had beneficial effects on hemodynamics and left ventricular function compared with metoprolol.7 At the moment, there is no available data concerning the relative impact of these 2 agents on long-term outcome in patients with chronic CHF.

The rationale for the use of $\beta$-adrenergic receptor antagonists in CHF is based on observations that sympathetic efferent neuronal activity is increased in CHF and that this sympathoexcitation has independent prognostic value.8,9 These drugs may provide cardiac protection in CHF via blockade of postjunctional $\beta$-adrenergic receptors on cardiac myocytes. Another mechanism by which $\beta$-blockers may be beneficial is through the antagonism of presynaptic $\beta_2$-adrenergic receptors, which facilitate neural norepinephrine release. In a previous report from our laboratory, we demonstrated an acute reduction in cardiac norepinephrine spillover with an intravenous infusion of the nonselective $\beta$-antagonist...

Received June 22, 2001; revision received August 22, 2001; accepted August 24, 2001.
From the Division of Cardiology, Department of Medicine, Mount Sinai Hospital, University of Toronto, Ontario, and the Section of Cardiology, Department of Medicine, St Boniface Hospital, University of Manitoba (E.R.A.), Winnipeg, Canada.
Correspondence to John D. Parker, MD, Associate Professor of Medicine, Division of Cardiology, Mount Sinai Hospital, University of Toronto, 600 University Ave, Suite 1609, Toronto, Ontario, Canada MSG-1X5. E-mail jdp@inforamp.net
© 2001 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org

2194
propranolol compared with the \( \beta_1 \)-selective antagonist metoprolol.\textsuperscript{10} Gilbert et al.\textsuperscript{11} examining results from previous placebo-controlled CHF studies, found that chronic therapy with carvedilol reduces coronary sinus norepinephrine levels whereas metoprolol does not. Both observations suggest that there may be important differences in the effect of selective versus nonselective \( \beta \)-adrenergic blockers on cardiac sympathetic efferent neuronal activity.

The purpose of the present experiment was to document the effect of chronic therapy with a selective versus a nonselective \( \beta \)-blocker on cardiac and systemic sympathetic efferent neuronal activity in patients with CHF. We hypothesized that the nonselective \( \beta \)-blocker carvedilol would cause a significant and larger reduction in cardiac norepinephrine spillover compared with the selective \( \beta_2 \)-adrenergic receptor antagonist metoprolol. In an effort to determine whether any observed change in spillover was mediated by prejuncional modulation of norepinephrine release versus a change in central sympathetic efferent neuronal outflow, we performed direct neural recordings as well as neurochemical assessments.

Methods

Patients

The study population consisted of 36 patients with a diagnosis of CHF. Included were patients who were between 18 and 80 years of age with symptoms of CHF and with left ventricular ejection fraction \(< 35\%\) and stable medical therapy for \( > 1 \) month. Exclusions were patients with an acute coronary syndrome or myocardial revascularization within the preceding 3 months, those who had a contraindication to \( \beta \)-blocker therapy, and those with primary valvular heart disease or systolic blood pressure \(< 85 \) mm Hg. In the carvedilol group, 15 patients were taking an ACE inhibitor and 2 patients were taking an angiotensin receptor blocker (ARB). In the metoprolol group, there were 13 patients taking an ACE inhibitor and 1 taking an ARB. Twelve patients in the carvedilol group and 12 in the metoprolol group were receiving a loop diuretic. The protocol was approved by the Ethical Review Committee for Human Experimentation of the University of Toronto.

Study Protocol

Patients who agreed to participate in this study were submitted to a right heart catheterization and measurements of cardiac and systemic norepinephrine kinetics. The microneurographic study was performed on the day preceding or subsequent to the cardiac catheterization in a quiet temperature-controlled room at the same time of the day with subjects resting supine. These measurements will be referred to as baseline measurements. Once baseline measurements were obtained, patients were randomized to carvedilol (\( n = 17 \)) or metoprolol (\( n = 18 \)) in a double-blind fashion. All patients were initiated on 3.125 mg of carvedilol or 6.25 mg of metoprolol twice a day and slowly uptitrated to a maximum dose of 25 mg of carvedilol or 50 mg of metoprolol twice a day. Patients were followed closely in the heart failure clinic until a maintenance dose of \( \beta \)-blocker was achieved and monthly thereafter until the completion of the study. After 4 months of therapy, repeat measurements of hemodynamics, norepinephrine kinetics, and microneurography were obtained. Thereafter, all patients were followed in a clinic by a physician not involved in the acquisition or analysis of these data.

Hemodynamic Measurements

Instrumentation for hemodynamic measurements included the insertion of a pulmonary artery catheter for recording right heart pressures and cardiac output. An arterial line was placed in the femoral or radial artery for blood sampling and measurement of arterial pressure. All pressures and electrocardiographic tracings were recorded on a strip chart recorder. A coronary sinus thermodilution catheter was inserted through the internal jugular or brachial vein and positioned using fluoroscopy. Five percent dextrose at room temperature was infused at 35 mL/min by a Harvard pump for coronary blood flow measurements, which were performed in triplicate.

Norepinephrine Spillover Measurements

Sympathetic efferent neuronal outflow was estimated by the measurement of cardiac and total body norepinephrine spillover, using techniques developed by Esler et al.\textsuperscript{12} that are well established in our laboratory.\textsuperscript{10} For these measurements, tritiated norepinephrine (1.6 \( \mu \)Ci/min with a 16-\( \mu \)Ci priming bolus of L-[2,5,6-\( \text{H} \)] norepinephrine; New England Nuclear) was infused into the femoral vein via a Harvard pump (model 33, Harvard Apparatus Canada) to steady-state concentration in plasma. Norepinephrine clearance and spillover rates were calculated as in our previous reports.\textsuperscript{10}

Analysis of Plasma Catecholamines

Plasma catecholamines were analyzed using high-performance liquid chromatography, as previously described.\textsuperscript{10} Fractions from the HPLC effluent containing tritium-labeled norepinephrine were assayed by liquid scintillation spectroscopy. Personnel blinded to patient status performed the biochemical analysis.

Muscle Sympathetic Nerve Activity

Blood pressure was measured from the right arm by an automatic cuff recorder. Heart rate was derived from lead II of the ECG. Muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve using the microneurographic technique, also well established in our laboratory.\textsuperscript{13} Blood pressure, lead II of the ECG, and MSNA were recorded simultaneously on paper and stored on computer for analysis with the use of a Laboratory View-based program (National Instruments). After instrumentation, subjects lay quietly for 15 minutes to achieve steady state before the recording signals were recorded over a 7-minute pre-\( \beta \)-blocker period. MSNA was expressed as bursts/min (burst frequency), bursts/100 cardiac cycles (burst incidence).

Statistical Analysis

All data are presented as mean\( \pm \)SEM. Statistical analysis was performed in Statview 5.0 (SAS Institute). Paired \( t \) tests were used for within group comparisons when data were distributed normally. Wilcoxon’s rank sum test was used when tests of normality failed. Between groups, comparisons were made using ANCOVA. Comparisons of baseline characteristics were made using unpaired \( t \) tests and the Fisher exact test. A \( P \) value \(< 0.05 \) was required for statistical significance.

Results

Baseline Characteristics

Baseline characteristics are shown in Table 1. All patients had New York Heart Association functional class II or III symptoms. The mean left ventricular ejection fraction (radionuclide angiography) was 19\( \pm \)2\% in the carvedilol group and

| TABLE 1. Baseline Characteristics |
|-------------------|-------------------|
| Carvedilol (\( n = 17 \)) | Metoprolol (\( n = 14 \)) |
| Age, y | 55\( \pm \)3 | 52\( \pm \)3 |
| Weight, kg | 90\( \pm \)4 | 86\( \pm \)5 |
| LVEF, % | 19\( \pm \)2 | 20\( \pm \)2 |
| NYHA class | 2.4\( \pm \)0.1 | 2.1\( \pm \)0.1 |

LVEF indicates left ventricular ejection fraction. Values are mean\( \pm \)SEM.
TABLE 2. Hemodynamic and Neurochemical Responses to Carvedilol and Metoprolol

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n=17)</th>
<th>Metoprolol (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 4 Months</td>
<td>Control 4 Months</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>81±2</td>
<td>66±2*</td>
</tr>
<tr>
<td>RA, mm Hg</td>
<td>4.4±0.9</td>
<td>2.1±0.6</td>
</tr>
<tr>
<td>PAmean, mm Hg</td>
<td>23±2</td>
<td>20±2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>13±2</td>
<td>11±1</td>
</tr>
<tr>
<td>FAS, mm Hg</td>
<td>125±6</td>
<td>132±6</td>
</tr>
<tr>
<td>FAD, mm Hg</td>
<td>67±3</td>
<td>68±4</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>58±5</td>
<td>64±4*</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.0±0.3</td>
<td>5.1±0.2</td>
</tr>
<tr>
<td>CSBF, mL/min</td>
<td>172±20</td>
<td>151±15</td>
</tr>
<tr>
<td>NEart, nmol/L</td>
<td>2.4±0.4</td>
<td>1.5±0.2*</td>
</tr>
<tr>
<td>NEcs, nmol/L</td>
<td>3.3±0.4</td>
<td>2.2±0.2*</td>
</tr>
<tr>
<td>TBNECL, L/min</td>
<td>2.1±0.1</td>
<td>2.0±0.1</td>
</tr>
<tr>
<td>TBNEESP, nmol/min</td>
<td>4.5±0.5</td>
<td>2.8±0.2*</td>
</tr>
<tr>
<td>NEesp, %</td>
<td>56±4</td>
<td>60±5</td>
</tr>
<tr>
<td>CANECL, L/min</td>
<td>55±7</td>
<td>52±6</td>
</tr>
<tr>
<td>CANESP, pmol/min</td>
<td>236±44</td>
<td>149±24*</td>
</tr>
</tbody>
</table>

RA indicates right atrial pressure; PAmean, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; FAS, femoral artery systolic pressure; FAD, femoral artery diastolic pressure; CSBF, coronary sinus blood flow; NEart, arterial plasma norepinephrine; NEcs, coronary sinus plasma norepinephrine; TBNECL, total body norepinephrine clearance; TBNEESP, total body norepinephrine spillover; NEesp, norepinephrine extraction rate; CANECL, cardiac norepinephrine clearance; and CANESP, cardiac norepinephrine spillover. Values are mean±SEM.

*P<0.05 versus control; †P<0.05 metoprolol versus carvedilol.

20±2% in the metoprolol group. Baseline heart rate was 81±2 bpm in the carvedilol group and 71±4 bpm in the metoprolol group, a difference that was statistically significant (Table 2; P<0.05). There were no significant differences in baseline mean pulmonary artery pressure, pulmonary capillary wedge pressure, arterial pressure, cardiac index, coronary sinus blood flow, total body, or cardiac norepinephrine spillover between the carvedilol and metoprolol groups.

Thirty-one patients completed the study, 17 in the carvedilol group and 14 in the metoprolol group. The mean maximum dose of study medication was 43±3 mg per day in the carvedilol group and 68±8 mg per day in the metoprolol group. Five patients did not complete the study. One patient died suddenly 4 weeks after randomization to carvedilol. Four patients assigned to the metoprolol group withdrew consent because of extreme fatigue from study medication (n=2) or for nonmedical reasons.

Changes in Concomitant Medication
As was specified in the protocol, changes in concomitant medication were kept to a minimum. The dose of vasodilator therapy was changed in 2 patients in the carvedilol group during the course of the study (increased in 1 and reduced in the other). The mean daily dose of furosemide was increased by 1±8 mg in the carvedilol group and decreased by 10±12 mg in the metoprolol group. These changes were not statistically significant.

Hemodynamic Responses to β-Blockade
Carvedilol caused a highly significant reduction in heart rate, from 81±2 to 66±2 bpm (P<0.001). There were no changes in filling pressures after 4 months of therapy with carvedilol (Table 2). Despite the absence of a significant change in systolic or diastolic arterial pressure, carvedilol led to an increase in pulse pressure from 61±5 to 69±5 mm Hg (P<0.01). Cardiac output did not change during the study. There was, however, a significant increase in stroke volume, from 62±4 to 79±5 mL (P=0.001).

Metoprolol also caused a significant reduction in heart rate, from 71±4 to 62±4 bpm (P=0.007). Except for a small increase in right atrial pressure, which was of no clinical significance, there were no other significant changes in filling pressures in response to metoprolol. As was observed with carvedilol, therapy with metoprolol was associated with a significant increase in pulse pressure, from 61±5 to 69±5 mm Hg (P=0.02). Cardiac output did not change in response to metoprolol, although there was a modest increase in stroke volume, from 73±5 to 82±8 mL (P=0.05).

Neurohormonal Response to β-Blockade
In the carvedilol group there was a large reduction in total body norepinephrine spillover, from 4.5±0.5 to 2.8±0.2 nmol/min (P<0.01; Table 2). There was no significant change in total body clearance of norepinephrine (2.1±0.1 versus 2.0±0.1 L/min, P=0.88). Cardiac norepinephrine
spillover was also significantly reduced from 236 ± 44 to 149 ± 24 pmol/min (P < 0.01; Table 2) after 4 months of therapy with carvedilol. There were no significant changes observed in the group taking metoprolol. Coronary sinus blood flow did not change significantly in either group (Table 2).

**Muscle Sympathetic Nerve Activity in Response to β-Blockade**

In patients who completed the microneurographic component of the study (carvedilol, n = 13; metoprolol, n = 10), there were no significant differences in age, sex, or other baseline characteristics between the carvedilol and the metoprolol groups. Table 3 shows the effect of 4 months of β-blockade on hemodynamic variables and MSNA. Neither carvedilol nor metoprolol affected blood pressure in these subjects. Both drugs lowered heart rate significantly, whereas there was no significant difference between the effect of carvedilol and metoprolol in this response. Neither β-adrenergic blocker altered MSNA.

**Discussion**

In the present study, two groups of heart failure patients were randomized in a double-blind fashion to 4 months of therapy with carvedilol or metoprolol. The nonselective β-adrenergic antagonist carvedilol caused a significant reduction in cardiac and systemic norepinephrine spillover, an effect that was not observed with the selective β₁-adrenergic receptor antagonist metoprolol (Table 2, Figure). We postulate that these significant reductions in cardiac and systemic norepinephrine spillover resulted from blockade of prejunctional β₂-adrenergic receptors associated with sympathetic efferent neurons that release norepinephrine. Studies performed in humans have suggested that prejunctional β₂-adrenergic receptors facilitate noradrenergic neurotransmission. It has been suggested that in states of chronic sympathoadrenal activation, such as chronic CHF, circulating epinephrine plays an important sympatoexcitatory role via its effects on prejunctional β₂-adrenergic receptors. Evidence for cardiac prejunctional sympathoexcitatory β₂-adrenergic receptors

<table>
<thead>
<tr>
<th>TABLE 3. Hemodynamics and Muscle Sympathetic Nerve Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (n=13)</td>
</tr>
<tr>
<td>Baseline 4 Months</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Hemodynamics</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>MSNA</td>
</tr>
<tr>
<td>MSNA/min</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>MSNA/100 heart beats</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; and MSNA, muscle sympathetic nerve activity. Values are mean ± SEM.
comes from studies in dogs, although this has been challenged. Human studies of cardiac sympathoexcitatory \( \beta \)-adrenergic receptors are limited. Recently, our laboratory provided evidence of cardiac sympathoexcitatory \( \beta \)-receptors using intracoronary infusions of salbutamol. Several placebo-controlled studies have demonstrated that nonselective \( \beta \)-adrenergic receptor blockade reduces plasma norepinephrine concentrations in patients with heart failure. Previous studies of the effects of \( \beta \)-selective adrenergic blockade on sympathetic efferent neuronal activity in the setting of heart failure have provided conflicting results.

It is possible that the observed decrease in systemic and cardiac norepinephrine spillover in response to carvedilol could have occurred secondary to a decrease in central sympathetic efferent neuronal outflow. This could have been mediated by the arterial baroreflex responding to the observed increase in arterial pulse pressure. This explanation would seem unlikely, because a similar increase in pulse pressure was observed in the metoprolol group. A direct, central sympathoinhibitory effect of \( \beta \)-adrenergic receptor blockade is also possible; such an effect has been suggested to contribute to the antihypertensive effect of these medications as well as their effects in chronic heart failure. Although this possibility has some appeal, particularly in light of the greater lipophilicity of carvedilol, it also seems unlikely, because the direct recording of muscle sympathetic nerve activity demonstrated no change in central sympathetic outflow. In light of these findings, we conclude that the reduction in systemic (total body) and cardiac norepinephrine spillover in the carvedilol group was a postganglionic effect, involving the release of norepinephrine that is regulated, in part, by prejunctional \( \beta \)-adrenergic receptors.

It is now recognized that facilitatory \( \beta \)-adrenergic receptors involved in the modulation of cardiac sympathetic activity may be located at more than one level within the sympathetic nervous system and not limited to a strictly presynaptic or prejunctional distribution. Armour and colleagues have demonstrated the presence and functional significance of intrathoracic ganglia and intrinsic cardiac sympathetic neurons. These neurons have been demonstrated to contain both \( \beta \)- and \( \beta \)-adrenergic receptors that are involved in neurotransmission and have sympathoexcitatory effects. Carvedilol may have caused more complete (\( \beta \) and \( \beta \)) \( \beta \)-adrenergic receptor blockade at the level of the intrathoracic ganglia and intrinsic cardiac neurons, providing another potential mechanism for the results observed.

It is important to discuss some limitations of our study. First, although the study was double blind and randomized, it was not placebo controlled. Therefore, it is not possible to account for the effect of time on the neurochemical endpoints. In light of this, it might be suggested that some of the sympathoinhibitory effects observed with carvedilol might not have been specific to the drug but, rather, an effect of time. This possibility seems unlikely, because there was no change in peripheral nerve activity during the course of the study. Although we did document a decrease in cardiac norepinephrine spillover, this is only an indirect measure of cardiac efferent sympathetic nerve traffic. Because it is not possible to directly measure efferent cardiac nerve activity in conscious humans, we cannot completely exclude a centrally mediated decrease in efferent cardiac sympathetic nerve activity. Finally, it cannot be concluded that potent reductions in sympathetic activity are associated with improved outcome in chronic heart failure. Indeed, the results of the MOXCON study using the central sympathoinhibitory agent, moxonidine, suggest that at some level reductions in sympathetic outflow may have adverse consequences.

In summary, in this randomized, double-blind study, we have demonstrated that therapy with carvedilol caused significant decreases in systemic and cardiac sympathetic activity whereas metoprolol did not. The importance of potential differences between different \( \beta \)-adrenergic blocking agents has been highlighted by the results of the recently published BEST study. These data provide a rationale for potential differences in the long-term impact of nonselective versus selective \( \beta \)-adrenergic antagonists on clinical outcome of patients with chronic CHF. Indeed, the results of the present study will be helpful in interpreting the results of ongoing comparative studies. If these studies demonstrate a favorable effect of a nonselective agent on outcome, then we provide a potential explanation. On the other hand, if no difference is observed with selective versus nonselective agents, then our results will call into question basic assumptions concerning the mechanism of treatment effects during long-term \( \beta \)-adrenergic blocking therapy in heart failure.

**Acknowledgments**

Dr Azevedo held a Research Fellowship Award from AstraZeneca/Heart and Stroke Scientific Research Corporation of Ontario. Dr Mak holds a Research Fellowship from the Canadian Institute for Health Research. Dr Newton holds a Research Scholarship Award. This study received financial support from GlaxoSmithKline and Roche Pharmaceuticals. The authors wish to thank the staff of the Bayer Cardiovascular Clinical Research Laboratory of the Mount Sinai Hospital for their help in the completion of these studies.

**References**

Nonselective Versus Selective β-Adrenergic Receptor Blockade in Congestive Heart Failure: Differential Effects on Sympathetic Activity
Eduardo R. Azevedo, Toshihiko Kubo, Susanna Mak, Abdul Al-Hesayen, Anne Schofield, Rebecca Allan, Susan Kelly, Gary E. Newton, John S. Floras and John D. Parker

Circulation. 2001;104:2194-2199
doi: 10.1161/hc4301.098282
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/104/18/2194

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/