Deterioration of Left Ventricular Chamber Performance After Bed Rest

“Cardiovascular Deconditioning” or Hypovolemia?

Merja A. Perhonen, MD, PhD; Julie H. Zuckerman, RN, RDMS; Benjamin D. Levine, MD

Background—Orthostatic intolerance after bed rest is characterized by hypovolemia and an excessive reduction in stroke volume (SV) in the upright position. We studied whether the reduction in SV is due to a specific adaptation of the heart to head-down tilt bed rest (HDTBR) or acute hypovolemia alone.

Methods and Results—We constructed left ventricular (LV) pressure-volume curves from pulmonary capillary wedge pressure and LV end-diastolic volume and Starling curves from pulmonary capillary wedge pressure and SV during lower body negative pressure and saline loading in 7 men (25±2 years) before and after 2 weeks of −6° HDTBR and after the acute administration of intravenous furosemide. Both HDTBR and hypovolemia led to a similar reduction in plasma volume. However, baseline LV end-diastolic volume decreased by 20±4% after HDTBR and by 7±2% after hypovolemia (interaction P<0.001). Moreover, SV was reduced more and the Starling curve was steeper during orthostatic stress after HDTBR than after hypovolemia. The pressure-volume curve showed a leftward shift and the equilibrium volume of the left ventricle was decreased after HDTBR; however, after hypovolemia alone, the curve was identical, with no change in equilibrium volume. Lower body negative pressure tolerance was reduced after both conditions; it decreased by 27±7% (P<0.05) after HDTBR and by 18±8% (P<0.05) after hypovolemia.

Conclusions—Chronic HDTBR leads to ventricular remodeling, which is not seen with equivalent degrees of acute hypovolemia. This remodeling leads to a greater decrease in SV during orthostatic stress after bed rest than hypovolemia alone, potentially contributing to orthostatic intolerance. (Circulation. 2001;103:1851-1857.)

Key Words: space flight ■ diastole ■ pressure ■ hypotension, orthostatic

Hydrostatic and hydrodynamic forces within the circulation determine the adequacy of left ventricular (LV) filling and subsequent stroke volume (SV) via the Starling mechanism. Postural changes alter the gravitational component of hydrostatic pressure, leading to large changes in the distribution of blood volume. For example, eliminating the head-to-foot gradient leads to a fluid shift from the legs to the chest of ≥1 liter, thereby acutely increasing right ventricular and LV transmural pressure,1–3 which increases diastolic filling and forward SV. This increase is only transient, however. Short-term activation of volume regulatory mechanisms by this central fluid shift results in a loss of plasma volume and the establishment of a new hemodynamic steady state with LV filling about halfway between upright and supine values within 24 to 48 hours.4,5 When gravitational gradients are subsequently restored, there is an excessive reduction in LV filling and SV in the upright position that ultimately leads to orthostatic hypotension in many individuals after long-term exposure to bed rest or space flight.5–9 Orthostatic hypotension and tachycardia have been observed with as little as 20 hours of head-down tilt bed rest,10 suggesting that the loss of plasma volume plays an essential role in mediating this hemodynamic response. However, volume infusion by itself has not been successful at restoring either supine11 or upright12 hemodynamics after more prolonged adaptation to bed rest. Combined with the failure of standard oral rehydration strategies to normalize orthostatic tolerance in astronauts,6,13 these observations raise the possibility that cardiac remodeling over time during bed rest may compound the loss of plasma volume and exacerbate the reduction in SV in the upright position. Recent work from this laboratory demonstrated that the heart becomes less “distensible” after 2 weeks of bed rest in −6° head-down tilt, resulting in diminished end-diastolic volume for any given filling pressure in the upright position.9 This apparent remodeling was accompanied by a reduction in plasma volume, thus SV was markedly reduced during orthostatic stress and blood pressure control was compromised. However, it is not certain whether this response is a specific cardiac adaptation to bed rest or simply a manifestation of hypovolemia with removal of pericardial constraint and alteration of right ventricular and LV chamber interactions.14 The purpose of this study was to compare the cardiac mechanical adaptation to bed rest directly with hypovolemia alone. Acute hypovolemia was
induced by intravenous furosemide in an amount sufficient to reproduce the same loss of plasma volume and reduction in ventricular filling pressure observed after bed rest in the same subjects.

**Methods**

**Subjects**
Seven sedentary, nonsmoking, healthy men aged 25 ± 2 years (range, 20 to 35 years; body mass index, 25 ± 0.6 kg/m²) participated in this study. All subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern and Presbyterian Hospital.

**Study Designs**

**Bed Rest Study**
Strict bed rest was done in the –6° head-down tilt position for a total of 18 days. Subjects were only allowed to elevate on one elbow for meals. Subjects were housed in the General Clinical Research Center at the University of Texas Southwestern Hospital and given a standard diet that consisted of 2796 ± 262 calories per day and included 5.0 ± 0.5 g of sodium per day. Fluids were allowed ad libitum, but intake and output were recorded. Figure 1 summarizes the study design. For more details, see Levine et al.5

**Acute Hypovolemia Study**
The same subjects who completed the bed rest study5 were recruited at least 1 year later; 7 of these 12 subjects agreed to return for the hypovolemia experiments. This prolonged period between studies was mandated to minimize fluoroscopy exposure in these healthy volunteers. However, a review of their medical history and physical activity over the previous year confirmed no intervening medical problems and no change in exercise habits. The protocol was repeated after intravenous furosemide administration 2 weeks after the baseline experiments to match the original design after bed rest (Figure 1).

**Measurements**

**Plasma Volume**
In the bed rest study, plasma volume was measured with the standard Evans blue dye technique5,6 during pretesting and on the 15th day of bed rest. In the acute hypovolemia study, plasma volume was measured at baseline using the same technique, and hematocrit was also measured. Two hours after furosemide administration, the change in plasma volume was calculated from the change in hematocrit.16

**Heart Rate and Blood Pressure**
Heart rate was monitored using the ECG (Hewlett-Packard). Blood pressure was measured continuously in the finger using photoplethysmography (Finapres, Ohmeda) and intermittently in the arm by electrophysigmanometry (Suntech 4240).

**LV End-Diastolic Pressure**
A 6-F balloon-tipped, fluid-filled catheter (Swan-Ganz, Baxter) was placed through an antecubital vein into the pulmonary artery under fluoroscopic guidance. All intracardiac pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero reading set at 5 cm below the sternal angle. The mean PCWP was determined visually at end expiration and was used as an index of LV end-diastolic pressure.5

**Stroke Volume**
Cardiac output was measured with a modification of the acetylene rebreathing technique using acetylene as the soluble and helium as the insoluble gas.5,17,18 SV was calculated from cardiac output and the heart rate measured during rebreathing.

**LV End-Diastolic Volume**
LV end-diastolic volume (LVEDV) was measured with 2D echocardiography using standard views and formulas, as recommended by the American Society of Echocardiography.19 Images were obtained with an annular phased-array transducer using a frequency of 2.5 to 3.5 MHz (Interspec Apogee CX). Measurements of LV endocardial areas were made from the parasternal short-axis window at the level of the mitral valve and papillary muscles and from the apical window in the 4-chamber view, where the major-axis distance was measured from the apex to the mitral annulus. To calculate LVEDV for each
subject, either a modified Simpson’s rule method or the area length method was chosen based on optimal endocardial definition. The same formula was used for each individual subject throughout the study.

**Testing Protocols**

**Protocol to Measure Starling Curves and the Pressure-Volume Relationship**
Cardiac filling was decreased by lower body negative pressure (LBNP), as previously reported. LBNP was implemented with a Plexiglas box sealed at the level of the iliac crest. Measurements of PCWP, cardiac output (and therefore SV), LVEDV, heart rate, and blood pressure were made after 5 minutes each of PCWP, cardiac output (and therefore SV), LVEDV, heart rate, and atrial pressure.

**Protocol for Maximal LBNP Tolerance Test**
Maximal orthostatic tolerance was measured using a ramped LBNP test, beginning at −15 mm Hg for 5 minutes and then increasing to −30 and −40 mm Hg for 5 minutes each, followed by an increase in LBNP by −10 mm Hg every 3 minutes until signs or symptoms of presyncope were achieved. LBNP tolerance was calculated from the summed product of the absolute magnitude of LBNP multiplied by time at each stage (mm Hg × min). LBNP tolerance was determined 3 days after the measurement of pressure-volume (P/V) relations before and after LBNP and saline infusion parts of the protocol before and after furosemide administration.

**Data Analysis**

**Starling Curves**
An index of the steepness of the Starling relationship (SV/PCWP) during decreases in cardiac filling was obtained by performing linear regression on the linear portion of the curve, including points obtained at baseline and during LBNP at −15 and −30 mm Hg. In previous studies, this characteristic was shown to predict a significant portion of the individual variation in LBNP tolerance. Starling curves were constructed both for each individual subject and for the grouped means for PCWP and SV.

**P/V Curves**
To evaluate chamber stiffness properties, we constructed P/V curves relating LVEDV to PCWP. For the purposes of the present study, we characterized and here define explicitly 3 different but related mechanical properties of the heart during diastole. (1) Specific dynamic stiffness (or its inverse, compliance) is used to mean the instantaneous change in pressure for a change in volume (dP/dV) at a specific LVEDV; (2) static stiffness or overall chamber stiffness (or its inverse, compliance) refers to the stiffness constant S of the logarithmic equation describing the P/V curve (see below); and (3) distensibility is used to mean the absolute LV end-diastolic volume at a given distending pressure, independent of dP/dV or S.

To characterize LV P/V relations, we modeled the data in this experiment according to the logarithmic equation described by Nikolic et al:

$$P = - S \ln[(V_m - V)/(V_m - V_0)]$$

where P indicates PCWP, V, LVEDV; V_m, the maximal volume obtained by this chamber; and S, a stiffness constant that describes the shape of the curve. The key feature of this model is the ability to identify the equilibrium volume of the left ventricle (ie, the LV volume when filling pressure is zero). This variable predicts the volume below which the LV must contract in systole to generate diastolic suction. Modeling of the logarithmic curves was performed with commercial software (Sigmaplot 2.01, Jandel Scientific). Initial values for iterative determination of the relationship were chosen for each individual subject as V_m = 1 mL above the maximum LVEDV observed during volume infusion and V_0 = 1 mL below the minimum LVEDV observed during LBNP. All curves were calculated for each individual subject before and after intervention for statistical comparison and for the composite curves relating the group mean LVEDV to the group mean PCWP for all subjects combined.

**Statistics**
Data are presented as means ± SE with n = 7 for both experimental conditions. Statistical probability was assessed with 2-way, repeated-measures ANOVA followed by Student’s paired t test to test the difference between the values before and after head-down tilt bed rest and before and after acute hypovolemia. P < 0.05 was considered statistically significant.

**Results**

**Cardiovascular Responses**
There was no statistical difference between the 2 interventions in the following baseline hemodynamic variables: mean arterial pressure, cardiac output, SV, total peripheral resistance, PCWP, right atrial pressure, and LVEDV (Table 1). Furosemide induced a diuresis of 1226 ± 76 mL of urine volume. Both bed rest (−15 ± 7%, P < 0.05) and acute hypovolemia reduced heart rate (5 ± 2%, P < 0.05), MBP (10 ± 2%, P < 0.01 vs before), MAP (10 ± 2%, P < 0.01 vs before), and LVEDV (8 ± 1%, P < 0.001 vs before). There were no significant changes in SV or total peripheral resistance. There were no significant changes in PCWP and LVEDV in response to furosemide administration.

Perhonen et al LV Performance After Bed Rest and Hypovolemia 1853

---

**TABLE 1. Subject Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Bed Rest Before</th>
<th>Bed Rest After</th>
<th>Change, %</th>
<th>Acute Hypovolemia Before</th>
<th>Acute Hypovolemia After</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>78 ± 3</td>
<td>78.5 ± 3</td>
<td>−1.9 ± 1.1</td>
<td>79.6 ± 3</td>
<td>78.5 ± 3</td>
<td>−1.4 ± 0.1</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77 ± 5</td>
<td>78 ± 3</td>
<td>4 ± 9</td>
<td>66 ± 2</td>
<td>64 ± 2</td>
<td>−3 ± 1</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>86 ± 2</td>
<td>90 ± 3</td>
<td>4 ± 2</td>
<td>90 ± 5</td>
<td>88 ± 3</td>
<td>−2 ± 1</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.8 ± 0.6</td>
<td>6.0 ± 0.4</td>
<td>−12 ± 6</td>
<td>6.6 ± 0.5</td>
<td>5.9 ± 0.3</td>
<td>−11 ± 3</td>
</tr>
<tr>
<td>Stroke volume, mL/min</td>
<td>92 ± 9</td>
<td>79 ± 4</td>
<td>−12 ± 7</td>
<td>100 ± 8</td>
<td>86 ± 7*</td>
<td>−14 ± 2</td>
</tr>
<tr>
<td>TPR, dynes · s · cm⁻¹</td>
<td>1091 ± 62</td>
<td>1241 ± 55</td>
<td>14 ± 5</td>
<td>1050 ± 85</td>
<td>1171 ± 92</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>10.7 ± 1.2</td>
<td>8.3 ± 0.9*</td>
<td>−21 ± 6</td>
<td>10.8 ± 0.7</td>
<td>7.4 ± 1.0*</td>
<td>−31 ± 7</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>8.1 ± 0.9</td>
<td>6.6 ± 0.8</td>
<td>−11 ± 16</td>
<td>8.2 ± 0.5</td>
<td>7.7 ± 1.0</td>
<td>−8 ± 12</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>148 ± 8</td>
<td>118 ± 7†</td>
<td>−20 ± 4</td>
<td>136 ± 6</td>
<td>127 ± 8*</td>
<td>−7 ± 2‡</td>
</tr>
</tbody>
</table>

Values are mean ± SE. MBP indicates mean arterial blood pressure; TPR, total peripheral resistance; and RAP, right atrial pressure.

*P < 0.05 and †P < 0.01 vs before, ‡P < 0.001 for interaction in two-way ANOVA.
volemia (-14±5%, \(P<0.05\)) led to similar reductions in plasma volume (Figure 2). Despite this similarity, baseline LVEDV decreased by 20±4% \((P<0.01)\) after bed rest and by 7±2% \((P<0.05)\) after acute hypovolemia (interaction \(P<0.001\), Table 1). Other hemodynamic parameters decreased similarly (Table 1). Maximal LBNP tolerance was not different between the groups at baseline, but it was reduced by 27±7% \((P<0.05)\) after head-down bed rest and by 18±8% \((P<0.05)\) after furosemide (Figure 3).

**Starling Curves**

Baseline PCWP decreased after bed rest by 21±6% and after acute hypovolemia by 31±7% \((P<0.05,\) Table 1). PCWP decreased during LBNP when compared with the baseline values under both conditions, and it increased during saline loading \((P<0.05)\), with no difference between interventions. Along with the decreased baseline PCWP and LVEDV, baseline SV was decreased by 12±7% \((P=0.09)\) with bed rest and by 14±2% \((P<0.05)\) with acute hypovolemia (Table 1). At any given LBNP level, SV was smaller \((P<0.05)\) after both conditions than at baseline. Starling curves (Figure 4) showed that the slope of the linear part of the curve calculated from the baseline supine position through both levels of LBNP was steeper after both bed rest and furosemide than at baseline. The slope increased from 4.97±0.28 to 9.15±1.20 mL/mm Hg \((P<0.05)\) for bed rest and from 5.70±0.67 to 7.13±1.09 mL/mm Hg \((P<0.05)\) for acute hypovolemia; this change was greater after bed rest than after furosemide (interaction \(P<0.05\) in 2-way ANOVA).

**P/V Curves**

After bed rest, P/V curves were shifted leftward, resulting in a decreased baseline LVEDV \((P<0.01)\) and a decreased volume for any given PCWP, without a significant change in S or overall static chamber stiffness (Figures 5 and 6). The equilibrium volume \((V_o)\) also decreased significantly after bed rest (from 80±8 to 50±9 mL, \(P<0.05\) for the comparison of the \(V_o\) derived from each individual subject’s curves, Table 2; note that the \(V_o\) illustrated in Figure 6A is derived from the logarithmic model of the group mean data points for
LVEDV and PCWP and thus differs from the mean of the individual values. In contrast to bed rest, with acute hypovolemia, the P/V curves were identical and V₀ was unchanged (55±10 to 56±8 mL, P=NS), despite a significant but smaller reduction in baseline LVEDV than after bed rest (Table 2 and Figure 6B).

Discussion

The principal new findings from the present study are that the leftward shift in the P/V relationship and the decreased equilibrium volume of the left ventricle that were found after 15 days of head-down tilt bed rest did not occur after a similar degree of hypovolemia induced acutely by intravenous furosemide. Although both conditions resulted in a similar reduction in plasma volume, supine LVEDV at baseline was reduced more after bed rest than after acute hypovolemia, providing additional evidence of LV remodeling during bed rest. Furthermore, SV was reduced more for a given change in filling pressure after bed rest than after acute hypovolemia. Thus, orthostatic intolerance tended to be more severe after bed rest, which included both sustained hypovolemia and physical inactivity, compared with acute hypovolemia alone.

Plasma Volume and Ventricular Filling Pressures

The present study showed that 15 days of head-down tilt bed rest and acute hypovolemia induced by furosemide led to similar reductions in plasma volume in the same subjects. This decrease in plasma volume is a well known consequence of head-down tilt bed rest or space flight,5,23,24 and it seems to be the proximate cause of the acute hemodynamic adaptation to microgravity. Thus, after a transient central fluid shift, volume-regulating mechanisms lead to a diuresis and/or a redistribution of intravascular volume; by 24 to 48 hours, a new hemodynamic equilibrium is established with a SV that stabilizes about halfway between the values observed in the upright and supine positions5,6 (ie, equivalent to an upright tilt angle of about 30°).

Although both head-down tilt bed rest and acute hypovolemia resulted in a decrease in LVEDV and SV when supine, this reduction was clearly greater after bed rest than after furosemide. This reduced cardiac filling led to a leftward shift of the diastolic P/V curve after bed rest such that LVEDV was smaller at any given filling pressure (including the equilibrium volume, or pressure = 0 mm Hg) and, therefore, was less "distensible."

A similar leftward displacement of the diastolic P/V curve has been observed after vasodilator25,26 administration, suggesting that peripheral pooling itself might modify LV diastolic function. Such drugs alter pericardial pressure by shifting blood between the heart and the systemic venous capacitance, thereby changing heart size and, necessarily, pericardial pressure.26 Several intracardiac and extracardiac factors contribute to overall LV diastolic function and the shape of the diastolic ventricular P/V curve.25,27 A recent study using sophisticated mathematical model analyses demonstrated that the pericardium modulates both flow-mediated and pressure-mediated atrioventricular interaction, thereby influencing hemodynamic profiles.28 However, in the present study, acute hypovolemia induced by furosemide did not alter the slope or zero intercept of the P/V curve; therefore, there was no short-term change in distensibility. Thus, it seems that in healthy humans in the supine position, pericardial constraint may play less of a role in determining LV filling pressure and volume than in dogs29 or patients with congestive heart failure.29 Therefore, we think it is unlikely that the leftward shift of the P/V curve after bed rest was due

---

**Figure 5.** P/V curves after head-down tilt bed rest (A) and acute hypovolemia (B) for representative individual. Curves relate LVEDV to PCWP derived from values obtained during LBNP (reduced LV filling) and saline infusion (increased LV filling). In each panel, 2 middle points represent 2 baseline values before LBNP and saline infusion. Computer-drawn curves are shown with data extrapolated to V₀ from logarithmic model.

**Figure 6.** P/V curves after head-down tilt bed rest (A) and acute hypovolemia (B) for all subjects. Curves are produced as in Figure 5. Stiffness constant (S) was determined from each curve using grouped mean data.

**TABLE 2.** Individually Derived Values of Equilibrium Volume, Maximum Volume, and Stiffness Constant

<table>
<thead>
<tr>
<th></th>
<th>Bed Rest</th>
<th>Acute Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>V₀, mL</td>
<td>80±8</td>
<td>50±9*</td>
</tr>
<tr>
<td>Vₘ, mL</td>
<td>266±57</td>
<td>208±44</td>
</tr>
<tr>
<td>S</td>
<td>17.6±3.4</td>
<td>19.8±8.9</td>
</tr>
</tbody>
</table>

Values are mean±SE. V₀ indicates equilibrium volume; Vₘ, maximum volume; and S, stiffness constant.

*P<0.05 vs before.
Implications for Orthostatic Tolerance

The relationship between SV and LV end-diastolic pressure (Frank-Starling mechanism) is a key factor governing the magnitude of the decrease in SV during orthostatic stress. Orthostatic intolerance is seen frequently after space flight or bed rest and is almost always associated with a reduced SV during orthostasis. Although the baroreflex response to this low SV may be impaired, upright heart rate, sympathetic activity, and vascular resistance have always been within a range that would provide adequate arterial pressure given the normal preadaptic SV.

Orthostatic tolerance has been only partially normalized, despite using volume loading before returning to earth and/or standing up, suggesting that tolerance is affected by factors other than changes in intravascular fluid status. For example, a recent study showed that LV atrophy and reduced distensibility, coupled with a reduction in plasma volume, altered ventricular performance during orthostatic stress after bed rest. This suggests that a reduction in plasma volume alone cannot explain all of the decreased SV after head-down tilt bed rest and/or exposure to microgravity.

A key observation of the present study was that the equilibrium volume of the LV was reduced after bed rest but not after hypovolemia alone. The equilibrium volume \( V_0 \) represents the volume below which the heart must contract in systole to generate a restorative force during relaxation to cause diastolic suction. We speculate that this loss of diastolic suction after bed rest is an important manifestation of cardiac remodeling that impairs ventricular filling to a greater extent after bed rest than acute hypovolemia alone. However, we must express some caution in this interpretation because the data for \( V_0 \) represent an extrapolation of our data beyond the last true data points obtained in this study. The actual difference in these values may be either more or less pronounced than is suggested by the extrapolation.

SV was consequently reduced to a greater extent for any change in PCWP (ie, steeper slope of the Starling curve) after long-term head-down tilt bed rest compared with acute hypovolemia alone. However, with hypovolemia alone, there was a shift to a more compliant portion of the same P/V curve (increased specific dynamic compliance) such that there was also a greater decrease in SV in the upright position compared with normovolemia. Thus, although the calculated LBNP tolerance was decreased consistently, with relative orthostatic intolerance after both conditions, the greater reduction in SV and steeper Starling curve during orthostatic stress after bed rest compared with acute hypovolemia led to a trend toward more severe orthostatic intolerance after bed rest. These results suggest that the cardiac remodeling associated with both inactivity and hemodynamic changes combines with the hypovolemia, leading to orthostatic intolerance after long-term bed rest.

In summary, this study shows that both bed rest and acute hypovolemia alone lead to a shift to a more compliant region on the diastolic P/V curve due to a lower ventricular volume. Thus, both conditions result in a prominent reduction in SV during orthostatic stress and reduced orthostatic tolerance. However, ventricular remodeling occurs during head-down tilt bed rest, leading to a decreased equilibrium volume of the left ventricle, reduced supine LVEDV, and compromised ventricular filling; these effects are clearly different from those of isolated acute hypovolemia. Despite similar reductions in LV filling pressures, the reduction in SV while in the upright position was greater after bed rest than after acute hypovolemia alone, potentially exacerbating orthostatic intolerance.

Acknowledgments

Supported by NASA SCORT grant NAGW-3582, NASA OLMSA grant NAG5-4846, and PHS M01 RR00633.

References


Deterioration of Left Ventricular Chamber Performance After Bed Rest: "Cardiovascular Deconditioning" or Hypovolemia?
Merja A. Perhonen, Julie H. Zuckerman and Benjamin D. Levine

Circulation. 2001;103:1851-1857
doi: 10.1161/01.CIR.103.14.1851

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/103/14/1851

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/