Effect of Aging and Physical Activity on Left Ventricular Compliance

Armin Arbab-Zadeh, MD; Erika Dijk, BS; Anand Prasad, MD; Qi Fu, MD, PhD; Pilar Torres, MD; Rong Zhang, PhD; James D. Thomas, MD; Dean Palmer, MS; Benjamin D. Levine, MD

Background—Left ventricular compliance appears to decrease with aging, which may contribute to the high incidence of heart failure in the elderly. However, whether this change is an inevitable consequence of senescence or rather secondary to reduced physical activity is unknown.

Methods and Results—Twelve healthy sedentary seniors (69.8±3 years old; 6 women, 6 men) and 12 Masters athletes (67.8±3 years old; 6 women, 6 men) underwent pulmonary artery catheterization to define Starling and left ventricular pressure-volume curves. Data were compared with those obtained in 14 young but sedentary control subjects (28.9±5 years old; 7 women, 7 men). Pulmonary capillary wedge pressures and left ventricular end-diastolic volumes by use of echocardiography were measured at baseline, during decreased cardiac filling by use of lower-body negative pressure (−15 and −30 mm Hg), and after saline infusion (15 and 30 mL/kg). Stroke volume for any given filling pressure was greater in Masters athletes compared with the age-matched sedentary subjects, whereas contractility, as assessed by preload recruitable stroke work, was similar. There was substantially decreased left ventricular compliance in healthy but sedentary seniors compared with the young control subjects, which resulted in higher cardiac pressures for a given filling volume and higher myocardial wall stress for a given strain. The pressure-volume curve for the Masters athletes was indistinguishable from that of the young, sedentary control subjects.

Conclusions—A sedentary lifestyle during healthy aging is associated with decreased left ventricular compliance, leading to diminished diastolic performance. Prolonged, sustained endurance training preserves ventricular compliance with aging and may help to prevent heart failure in the elderly. (Circulation. 2004;110:1799-1805.)

Key Words: aging ■ diastole ■ exercise ■ hemodynamics ■ myocardium

Heart failure is the leading cause of hospitalizations for patients over the age of 65 years, resulting in substantial morbidity, mortality, and cost. Although coronary artery disease and other comorbid conditions often lead to impaired ventricular function in this population, up to 50% of elderly heart failure patients have a normal ejection fraction. In such patients, reduced left ventricular (LV) compliance, or “diastolic dysfunction,” is presumed to play a significant role. Drawing primarily from animal studies, recent reviews have suggested that diastolic function deteriorates with age. Moreover, indirect measures of “diastolic function,” such as mitral filling velocities, have been reported to decline with age in population-based studies, suggesting that the human heart may also stiffen during aging. 

However, cardiac compliance has never been measured directly in completely healthy, asymptomatic elderly volunteers. Furthermore, recent work suggests that bed rest deconditioning impairs and endurance training improves cardiac compliance. Therefore, we hypothesized that sedentary aging results in decreased LV compliance, whereas endurance training during healthy aging preserves ventricular compliance.

Methods

Subject Population

Twelve healthy adults older than 65 years of age (6 female, 6 male; mean age, 69.8±3 years; all white) formed the sedentary seniors group, and 12 age-matched Masters athletes (6 female, 6 male; mean age, 67.8±3 years; all white) represented the athletic group. All subjects were rigorously screened for the presence of arterial hypertension, obstructive coronary artery disease, or structural heart disease by use of 24-hour blood pressure recordings, baseline and exercise ECGs, and echocardiograms. Body fat content and lean body mass were measured by underwater weighing. Masters athletes were recruited from race records derived from United States Masters Athletics—sanctioned events demonstrating consistent age-group place winners at regional and national endurance races for at least 10 years. The athletic subjects ultimately recruited had participated in regular endurance competitions for 23±8 years, with a weekly running mileage of 32±10 miles or equivalent swimming or
cycling. Six of the Masters athletes were nationally ranked competitors, and 6 were regional champions. Sedentary participants, conversely, were excluded if they engaged in endurance exercise for more than 30 minutes 3 times a week.

Subjects of either group were excluded if one of the following was present: mean daytime blood pressure greater than 140/90 mm Hg, ECG changes suggestive of ischemic heart disease, left bundle-branch block, atrial flutter/fibrillation, atrioventricular block greater than first degree, baseline or exercise-induced wall motion abnormalities, valvular heart disease other than mild valvular insufficiency, right or LV hypertrophy (by ECG or echocardiogram, only in sedentary subjects), untreated thyroid disorders, chronic lung disease, regular cigarette smoking within the previous 10 years, body mass index of 30 or greater, cardiovascular medication, or warfarin use. In addition, 14 healthy, sedentary young subjects (7 female, 7 male; mean age, 28.9±5 years) who were studied before this investigation in our laboratory according to the same standards and criteria were used for comparison. All subjects signed an informed consent approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

Echocardiography
Baseline and exercise echocardiographic evaluations were performed to detect structural or ischemic heart disease (HDI 5000, ATL). In addition, LV end-diastolic volumes and end-systolic volumes were measured by use of the modified Simpson’s rule method during altered loading conditions of the experimental protocol as described below. Great care was taken to avoid foreshortening of image views and to record images with optimal endocardial definition. All images were stored digitally for offline analysis. Echocardiographic images were analyzed locally by an unblinded investigator and by an independent core laboratory, whose analysts were blinded to the study protocol and results. Results from both analyses were compared for variation. In addition, echocardiographic assessment of LV end-diastolic volume was compared with analysis by MRI.

Peak Oxygen Consumption
A modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity. Measures of ventilatory gas exchange were made by use of the Douglas bag technique. Gas fractions were analyzed by mass spectrometry, and ventilatory volume was measured by use of a Tissot spirometer. Maximum oxygen uptake was defined as the highest oxygen uptake measured from at least a 40s Douglas bag. Heart rate was monitored continuously via ECG, and cardiac output was measured by use of a modification of the acetylene rebreathing technique at baseline, steady state 1 (~30% maximum oxygen uptake), steady state 2 (~60% maximum oxygen uptake), and at peak exercise.

Cardiac Catheterization and Experimental Protocol
A 6F balloon-tipped fluid-filled catheter was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. The wedge position of the catheter was confirmed by both fluoroscopy and the presence of typical waveforms. Mean pulmonary capillary wedge pressure and right atrial pressures were determined visually at the end of expiration. Cardiac output was measured by use of the acetylene rebreathing technique at baseline, steadystate 1 (~30% maximum oxygen uptake), steady state 2 (~60% maximum oxygen uptake), and at peak exercise.

Cardiac MRI Measurements
MRI was performed on a 1.5-T Philips NT MRI scanner. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 ms were obtained to calculate LV masses and volumes as previously described. LV mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/mL. For LV volume determination, the endocardial border of each slice was identified manually at end diastole and end systole, and volumes were calculated by summation. End diastole was defined as the first frame in each sequence and end systole as the frame with smallest endocardial area. LV volumes were calculated by use of the Simpson’s rule technique as previously described. LV ejection fraction was computed according to the formula (end-dia-
TABLE 1.  Subject Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sedentary Seniors</th>
<th>Masters Athletes</th>
<th>Young Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.8 ±3</td>
<td>67.8 ±3</td>
<td>28.9 ±5‡</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.3 ±10.1</td>
<td>170.0 ±11.3</td>
<td>173.7 ±5.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.3 ±10.6</td>
<td>64.6 ±13.5*</td>
<td>71.2 ±4.4</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87 ±0.16</td>
<td>1.78 ±0.23</td>
<td>1.83 ±0.16</td>
</tr>
<tr>
<td>% Body fat</td>
<td>28.7 ±7.2</td>
<td>17.6 ±5.8*</td>
<td>22.5 ±4.3*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66 ±9</td>
<td>52 ±6*‡</td>
<td>66 ±2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123 ±10</td>
<td>117 ±12</td>
<td>121 ±8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73 ±6</td>
<td>69 ±7</td>
<td>72 ±5</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.85 ±0.63</td>
<td>5.57 ±1.21</td>
<td>6.66 ±1.31+</td>
</tr>
<tr>
<td>Cardiac index, L · min⁻¹ · m⁻²</td>
<td>2.63 ±0.31</td>
<td>3.22 ±0.61*</td>
<td>3.50 ±0.49*</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>70.8 ±14</td>
<td>95.8 ±21*</td>
<td>98.7 ±19*</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>38.2 ±6</td>
<td>54.8 ±8*</td>
<td>52.7 ±8*</td>
</tr>
<tr>
<td>VO₂max, mL · kg⁻¹ · min⁻¹</td>
<td>21.6 ±2.8</td>
<td>38.6 ±6.1*</td>
<td>39.5 ±4.9*</td>
</tr>
<tr>
<td>Arterial elastance, mm Hg/mL</td>
<td>1.82 ±0.45</td>
<td>1.21 ±0.27*</td>
<td>1.07 ±0.20*</td>
</tr>
<tr>
<td>Relative LV mass, g/m²</td>
<td>69.2 ±11</td>
<td>82.9 ±18*</td>
<td>90.6 ±16*</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>104 ±24</td>
<td>140 ±33*</td>
<td>119 ±19</td>
</tr>
<tr>
<td>LV end-diastolic volume index, mL/m²</td>
<td>56 ±10</td>
<td>80 ±12‡</td>
<td>63 ±6</td>
</tr>
<tr>
<td>Mass-to-volume ratio</td>
<td>1.27 ±0.31</td>
<td>1.08 ±0.26‡</td>
<td>1.40 ±0.24</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>70.0 ±3.3</td>
<td>71.7 ±5.1</td>
<td>74.3 ±4.2</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.

*Statistically significant difference from sedentary seniors; †statistically significant difference from Masters athletes; ‡statistically significant difference from young controls. Blood pressure values were obtained from 24-hour blood pressure monitoring; stroke volume was calculated from heart rate and cardiac output obtained from acetylene rebreathing technique; LV mass, volume, and ejection fraction were derived from MRI data. VO₂max indicates maximum oxygen uptake; EDV, end-diastolic volume.

Results

Subject Characteristics

Baseline data are presented in Table 1. Sedentary seniors and athletic subjects were well matched for age. As expected, weight, body fat, and resting heart rate were lower in the Masters athletes, but stroke volume was greater compared with sedentary subjects, resulting in a similar cardiac output. Mean arterial stiffness (effective arterial elastance) was greater in the sedentary seniors than in both Masters athletes and young control subjects, indicating a higher arterial load, despite similar average 24-hour systolic and diastolic blood pressures. Baseline ejection fraction was not different between the groups. As expected, athletes achieved higher maximum oxygen uptakes compared with the age-matched sedentary subjects.

Cardiac Remodeling

LV end-diastolic volume and mass were greater in the Masters athletes compared with the sedentary seniors (Table 1). Echocardiographic and MRI assessments of end-diastolic volume yielded excellent correlation (r=0.9; slope 0.9; P<0.001; 95% confidence limits, 9.2 to 15.0; coefficient of variation, 12.5%). There was a trend for a greater LV mass-to-volume ratio for the sedentary seniors, which did not reach statistical significance.

Figure 1. Systolic ventricular performance for sedentary seniors (n=12) and Masters athletes (n=12). Shown are mean group data ± SEM for stroke volumes at given pulmonary capillary wedge pressures (A) and for estimated stroke work at given LV end-diastolic volumes (B). Data points correspond to 2 degrees of lower-body negative pressure, 2 baselines, and 2 saline infusions. Lines represent results of second linear (A) and linear (B) regression analyses (r=0.97 and 0.95 for sedentary subjects and 0.99 and 0.98 for athletes, respectively, P<0.01 for all). Note substantially lower stroke volume for any given filling pressure in sedentary seniors, whereas their preload recruitable stroke work was similar compared with Masters athletes, indicating equivalent contractile function.
Diastolic pressure-volume curves. A, Pressure-volume curves for sedentary seniors (n=12, r=0.98), young control subjects (n=14, r=0.95), and Masters athletes (n=12, r=0.94). B, Same data when estimated transmural pressures (pulmonary capillary wedge pressure—right atrial pressure) are used instead of pulmonary capillary wedge pressures (r=0.93 for sedentary seniors, r=0.95 for young control subjects, r=0.94 for athletes). Given are mean group data ±SEM (horizontal bars, volume; vertical bars, pressure). Data points correspond to 2 degrees of lower-body negative pressure (LBNP, lower data points), baseline 2 and 1 (third and fourth data points from below), and 2 saline infusions (2 upper data points). Note left shift and steeper slope of curve for sedentary senior subjects compared with Masters athletes and young control subjects, suggesting a less distensible, stiffer ventricle (A). Disparity between sedentary seniors and 2 other groups persisted with use of estimated transmural pressures, confirming a difference in ventricular compliance (B).

Cardiac Mechanics

Elderly athletes were able to generate a higher stroke volume for any given filling pressure than sedentary seniors (Figure 1A). Importantly, this was achieved without evidence for better contractile function (Figure 1B). The preload recruitable stroke work for the sedentary seniors was not significantly different from that of the athletes, suggesting equivalent contractile function. The hemodynamic responses to changes in volume loading for both groups are given in Table 2. Norepinephrine release at baseline and during unloading was not different between the groups (Table 2), and changes in heart rate and blood pressure over the range of filling pressures were also similar, consistent with similar neurohumoral activation during the protocol.

The pressure-volume curves confirmed a substantially greater LV compliance for the Masters athletes compared with the sedentary seniors (Figure 2A). The constant “a,” which describes the chamber stiffness for the group mean data, was 0.039 for the athletes, compared with 0.055 for the sedentary seniors, suggesting greater ventricular stiffness for the latter. The curve for the young sedentary group was virtually identical to that of the elderly athletes and also revealed a more compliant ventricle (a=0.036) compared with the elderly sedentary subjects. Individual comparisons of “a” confirmed the difference between the groups (average “a” was 0.029±0.026 and 0.013±0.020 for sedentary seniors and Masters athletes, respectively; P=0.05). Multivariate analysis likewise confirmed that the pressure-volume curves for the Masters athletes were clearly different from those of the sedentary seniors (P<0.0001), whereas there was no statistically significant difference between athletes and young control subjects. Equilibrium volumes for sedentary seniors, Masters athletes, and young control subjects were 12.3, 39.7, and 26.7 mL, respectively.

Because extraventricular forces influence resting ventricular volumes and pressures,25 we also calculated the relationship between estimated transmural pressures (pulmonary capillary wedge pressure—right atrial pressure) and LV end-diastolic volume (Figure 2B). The difference between the groups persisted when estimated transmural pressures were used, supporting the validity of a true difference in ventricular compliance (Figure 2B). Finally, as derived from the LV end-diastolic stress-strain relationship (Figure 3), at any given degree of deformation, the ventricles of the sedentary subjects developed greater wall tension than those of the fit subjects. This relationship reached statistical significance during the 2 levels of saline infusion, with a rapid divergence of the stress-strain curves (P=0.002).

Discussion

The key new findings from the present study include the following. (1) Healthy but sedentary seniors exhibited substantially greater LV stiffness compared with healthy, sedentary young control subjects, providing evidence that cardiac
Aging and Left Ventricular Compliance

Aging is associated with numerous changes and adaptations in the cardiovascular system. Vascular and ventricular wall thickness increase, whereas arterial compliance, endothelial function, and ventricular contractility decline. Each of these changes is related to an increase in cardiovascular morbidity and mortality. There is controversy, however, about to what extent these adaptations are of intrinsic nature, ie, part of a “natural” aging process, or a response to environmental factors, such as accumulating toxins and/or an age-related change of behavior by the host organism. Because humans and animals alike adopt a more sedentary lifestyle with aging, it is conceivable that some of the observed cardiovascular adaptations are related to decreased physical activity. For example, bed rest deconditioning leads to many of the apparent manifestations of the aging process, such as decreased work capacity, increased sympathetic nerve activity, and muscle atrophy. Furthermore, 2 weeks of bed rest results in decreased cardiac volume and distensibility, resulting in a diminished stroke volume, contributing, at least in part, to orthostatic intolerance. More prolonged bed rest (6 to 12 weeks) leads to “physiological” atrophy of the heart of at least 10% to 15% of LV mass, which may further compromise diastolic function. In fact, recent longitudinal data suggest that 3 weeks of bed rest causes a greater deterioration in maximal work capacity than 30 years of aging. The results of the present study show that aging in healthy adults is associated with ventricular chamber and myocardial stiffening, which can be prevented with prolonged and sustained endurance exercise.

In addition to active ventricular relaxation during diastole, adequate ventricular compliance is essential for efficient cardiac filling. Ventricular chamber stiffness is determined primarily by the viscoelastic properties of the myocardium, ventricular mass, chamber geometry, and pericardial constraint. Aging is associated with alteration of size, number, and structure of cytoskeletal proteins and extracellular components, which contributes to increased viscoelastic myocardial stiffness, as demonstrated in our study. This alteration is assumed to be a response to increasing vascular load observed with aging, similar to the more apparent changes in LV hypertrophy in response to arterial hypertension. Chamber stiffness is increased in pathological concentric ventricular hypertrophy. However, it appears that as long as the myocardial viscoelastic properties are maintained, ie, no fibrotic changes are present, this increased stiffness is rather the result of an altered mass-to-volume ratio than an increase in mass per se. In the present study, the Masters athletes had considerably greater LV mass, as measured by MRI, than their sedentary counterparts, yet still had reduced LV stiffness and improved compliance. These results are similar to those reported by our group cross-sectionally in endurance athletes and longitudinally with prolonged endurance training.

It is important to note, however, that the relative LV mass of the Masters athletes was not significantly different from that of the young control subjects, arguing that LV mass was maintained during aging with lifelong exercise, rather than hypertrophied. However, their volume was somewhat larger, leading to the smallest mass/volume ratio of all 3 subject groups (Table 1). In contrast, the sedentary seniors had significantly smaller LV volumes, which has been observed by others. The functional consequences of this difference in chamber geometry include increased chamber stiffness, reduced chamber distensibility, and diminished ventricular performance. Moreover, the analysis of the myocardial stress-strain relationship confirmed that intrinsic myocardial stiffness increases with aging, at least in part because of a sedentary lifestyle. Together, these results further suggest that the stiffening of the myocardium and the reduced chamber distensibility of sedentary aging can be effectively offset or prevented by favorable ventricular remodeling maintained by exercise training.

Adequate ventricular chamber compliance is important to allow cardiac filling at low pressures as well as to increase cardiac output via the Frank-Starling mechanism. In this study, lower LV compliance in healthy elderly subjects was associated with higher ventricular pressures after cardiac loading compared with age-matched athletic individuals or young control subjects. Such stiffening of the ventricle may decrease the threshold for dyspnea and heart failure in the setting of myocardial insults such as ischemia, hypertension, or metabolic derangement, all of which lead to further decrease of cardiac compliance. Stiff ventricles in heart failure patients with preserved ejection fraction have been shown to induce high cardiac filling pressures and to impair augmentation of end-diastolic volume with exercise, leading to reduced exercise tolerance and dyspnea. Preservation of ventricular compliance may therefore help to prevent this common type of heart failure.

The mechanisms leading to the demonstrated preservation of ventricular compliance with endurance training probably include preservation of viscoelastic myocardial properties.
and pericardial size, as well as optimization of chamber geometry. Prolonged endurance exercise is known to result in eccentric ventricular hypertrophy, ie, a balanced enlargement of ventricular mass and dimensions. These adaptations lead to profoundly improved cardiac performance without apparent change in contractility, which thus is largely explained by enhanced diastolic function. In addition, prolonged exercise training may elicit its effect through maintenance of vascular elasticity and thus smaller arterial load. For example, in the present study, effective arterial elastance was greater in sedentary compared with fit elderly subjects. Arterial elastance is inversely related to vascular compliance and has been shown to be a more sensitive marker for arterial load than total peripheral resistance. Decreased vascular compliance is associated with aging and hypertension and recently has been related to heart failure with preserved ejection fraction as well as to cerebrovascular events. Endurance training preserves vascular elasticity with aging, as confirmed in our study, and thereby may prevent cardiac adaptive changes, ie, alteration of myocyte morphology or focal proliferation of matrix, which lead to increasing myocardial stiffness. Therefore, the present results support the concept that preserving ventricular–vascular coupling is a key component in the fight against hypertension and heart disease.

One limitation of our investigation was the use of mean pulmonary capillary wedge pressure as a surrogate for LV end-diastolic pressure. In the absence of mitral valve disease, as ensured in our study, pulmonary capillary wedge pressure is a reasonable approximation of left atrial and ventricular end-diastolic pressure. However, mean wedge pressure may be affected by fluctuations of left atrial pressure, induced by variations of LV filling time, which are not necessarily reflected in LV end-diastolic pressure. Moreover, animal models have demonstrated slowing of myocardial relaxation with aging, which may be ameliorated by exercise training. This delayed filling not only may distort the atrial pressure waveform during diastole but also may result in incomplete relaxation, leading to higher left atrial and LV filling pressures, particularly because heart rates were somewhat higher in the sedentary compared with the trained subjects.

However, arguing against this hypothesis is the fact that the primary differences between the young and older sedentary pressure-volume curves occurred during increases in LV filling from –30 mm Hg lower-body negative pressure (the smallest volume and lowest pressure) through baseline, when the heart rate was decreasing, rather than increasing (Table 2). Although we did indeed observe a typical Bainbridge reflex with a nonneural increase in heart rate at the highest-volume infusion level in all 3 groups, at this point, the curve is influenced predominantly by pericardial constraint, and the slope of all 3 curves is essentially vertical between these 2 points. Moreover, any increase in heart rate during the highest volume load was modest at best and was unlikely to alter the diastolic filling period substantially, with clear periods of diastasis in both Doppler and pressure waveforms observed at all points. Thus, it is very unlikely that the substantial differences among the curves could be a result of heart rate–mediated alterations in ventricular relaxation.

In conclusion, a sedentary lifestyle is associated with a decline of ventricular compliance, leading to higher cardiac filling pressures and lower stroke volumes for a given filling volume compared with age-matched athletes or young individuals. Prolonged, sustained endurance training preserves ventricular compliance with aging and may be an important approach to reduce the probability of heart failure with aging.

Acknowledgments

This study was supported by National Institutes of Health grant AG17479-02. The authors thank Sarah Witkowski, MS, Julie H. Zuckerman, RN, Kimberly Williams, RN, and Marta Newby, RN, for their help with the data collection, and Tanja Taivassalo, PhD, for critical review of the manuscript (all at the Institute for Exercise and Environmental Medicine, Dallas, Tex); and Donna E. Levy, MS (Dana-Farber Cancer Institute, Boston, Mass), for her help with the statistical analysis. In addition, the authors thank Edward Yellin, PhD (Albert Einstein College of Medicine, Bronx, NY) for his critique of the manuscript and valuable suggestions.

References

Effect of Aging and Physical Activity on Left Ventricular Compliance
Armin Arbab-Zadeh, Erika Dijk, Anand Prasad, Qi Fu, Pilar Torres, Rong Zhang, James D. Thomas, Dean Palmer and Benjamin D. Levine

Circulation. 2004;110:1799-1805; originally published online September 13, 2004;
doi: 10.1161/01.CIR.0000142863.71285.74
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/110/13/1799

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/