Evaluation of Left Ventricular Filling Pressures by Doppler Echocardiography in Patients With Hypertrophic Cardiomyopathy

Correlation With Direct Left Atrial Pressure Measurement at Cardiac Catheterization

Jeffrey B. Geske, MD; Paul Sorajja, MD; Rick A. Nishimura, MD; Steve R. Ommen, MD

Background—Diastolic dysfunction is a major pathophysiological abnormality in hypertrophic cardiomyopathy (HCM). Doppler echocardiographic parameters correlate with left ventricular (LV) filling pressures in other diseases, but it is unclear whether these findings apply to patients with HCM, who have multiple complex interrelated events leading to diastolic dysfunction. This study compares Doppler echocardiographic estimates of filling pressures to direct measurements of left atrial pressure (LAP) via catheterization in 100 patients with HCM.

Methods and Results—One hundred patients who were symptomatic with HCM (New York Heart Association class III/IV, 82%) underwent measurement of early diastolic transmitral flow velocity (E) and mitral annular velocities (e') with the use of transthoracic echocardiography within 48 hours of cardiac catheterization with direct measurement of LAP. In a subset of 42 patients, echocardiographic and catheterization measurements were performed simultaneously. Mean LAP directly correlated with medial E-e' ratio in the overall population (r=0.44, P<0.0001) and also in the subgroup of patients who had simultaneous echocardiographic and catheterization studies (r=0.28, P=0.07). However, scatter was present. A calculated mean LV filling pressure was derived from the E-e' ratio with the use of a previously described regression equation, and the 95% confidence limits of agreement with measured mean LAP exceeded ±18 mm Hg both for the overall group and for the subgroup who had simultaneous studies. Similar results were obtained with the lateral E-e' ratio. Only 1 patient had a previously defined “normal” E-e' ratio of <8.

Conclusions—In symptomatic patients with HCM, Doppler echocardiographic estimates of LV filling pressure with the use of transmitral flows and mitral annular velocities correlate modestly with direct measurement of LAP. Given the complex nature of diastolic dysfunction in HCM, precise characterization of LV filling pressure in an individual patient cannot be determined with the use of these noninvasive parameters. (Circulation. 2007;116:2702-2708.)

Key Words: cardiomyopathy ▪ catheterization ▪ diastole ▪ echocardiography ▪ hypertrophy

Diastolic dysfunction is a major contributor to the underlying pathophysiology in patients with hypertrophic cardiomyopathy (HCM).1 Diastolic dysfunction is the sum total of a complex sequence of multiple interrelated events, including prolonged ventricular relaxation, loss of ventricular suction, increased myocardial fibrosis, and increased chamber stiffness, that result in symptoms of angina and dyspnea. In the past, cardiac catheterization was required to determine the extent of diastolic dysfunction by direct measurement of left ventricular (LV) filling pressures. The development of noninvasive Doppler indices including transmitral flow velocities and tissue Doppler imaging (TDI) has allowed noninvasive estimation of filling pressures in patient populations other than HCM.2-4 However, studies that have attempted to correlate filling pressures with these noninvasive indices in HCM have led to mixed results.5-10 The objective of this study was to examine the clinical utility of currently available Doppler echocardiographic measurements in the assessment of LV filling pressures in HCM, with correlation of direct measures of left atrial pressure (LAP) at cardiac catheterization.

Editorial p 2662
Clinical Perspective p 2708

Methods

Patient Population

This study was approved by the Mayo Foundation institutional review board. Between January 2000 and April 2007, 115 patients with HCM in normal sinus rhythm underwent comprehensive 2-dimensional transthoracic echocardiogram (TTE) within 48 hours of hemodynamic cardiac catheterization with direct measurement of
LAP. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic etiologies. Patients were excluded from the study for the following criteria: poor TTE quality (n=7), prior cardiac surgery (n=4), and prior septal ethanol ablation (n=4), leaving a final study population of 100 patients. Forty-two patients underwent simultaneous measurement of echocardiographic and catheterization parameters. Clinical indications for cardiac catheterization were percutaneous septal ethanol ablation in 55 patients and diagnostic hemodynamic evaluation in 45 other patients. All patients provided informed consent for review of their medical records in accordance with Minnesota law. All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Invasive Hemodynamic Study

All invasive studies were performed in a fasting state with conscious sedation. Cardioactive medications were continued on the day of the procedure. Femoral venous access was used to gain access to the right heart. LAP was directly measured via transseptal puncture with placement of an 8F Mullins sheath into the left atrium. High-fidelity, micromanometer-tip catheters (Millar Instruments, Houston, Tex) were used in 55 patients as previously described. Fluid-filled catheters were used in the remaining patients. All invasive hemodynamic measurements were acquired at steady state from end-expiratory cycles before septal alcohol ablation or administration of cardiotropic medications. For 92 patients, rapid-acquisition (5-ms intervals) digital records were employed for data collection and subsequent offline analysis. In 8 patients, paper records were scanned, scaled, and analyzed with the use of a set pixel-to-height ratio. The following variables were derived: LAP, left ventricular end-diastolic pressure (LVEDP) (Figure 1). In addition, minimum LV pressure, peak –dP/dt, and the time constant of relaxation were analyzed in patients who underwent catheterization with high-fidelity, micromanometer-tip catheters (55 patients). The time constant of LV relaxation was calculated by the method of Weiss et al.15

Echocardiographic Measurements

All echocardiographic data were averaged from 3 to 5 end-expiratory cycles. LV cavity size, wall thickness, and ejection fraction were measured in accordance with American Society of Echocardiography recommendations. Left atrial volume was measured from 2 orthogonal views as previously described.12,13 Mitral inflow velocity curves and annular TDI signals were obtained as previously described (Figure 1). Peak Doppler velocities were analyzed to determine early (E) and late (A) diastolic flow across the mitral valve. Mitral regurgitation was graded as none/trivial, mild, moderately severe, or severe by combined analysis of jet area, jet width, and spectral Doppler intensity. TDI from the lateral annulus was obtained from the apical 4-chamber view, and peak early tissue Doppler velocities of the mitral mitral annulus (medial e') were analyzed. In 42 patients who had simultaneous echocardiographic and catheterization studies, the peak early tissue Doppler velocity of the lateral mitral annulus (lateral e') was also obtained.

Data Analysis

Continuous variables are expressed as mean±SD. Correlation of continuous variables was examined with simple linear regression analysis. Two-sample Student t tests, χ² analyses, and Fisher exact tests were used as appropriate. Receiver operating characteristic (ROC) curves were generated to assess the correlation of the E-e' ratio with mean LAP for mean LAP ≥15 mm Hg and mean LAP ≥20 mm Hg. The area under the curve (AUC) was reported as mean±SD.

Bland-Altman analysis with 95% confidence limits of agreement was used to compare pressure measurements. A previously described regression equation derived from patients with HCM with the use of the lateral e' velocity ([LV pre-A]=1.1×[E-e' ratio]+3.2) was used to estimate LV filling pressure; comparisons of estimated LV filling pressure and directly measured mean LAP were

Figure 1. Composite diagram of pressure tracings and Doppler velocities. Top left, High-fidelity pressure tracing of LV, left atrium (LA), and aorta (Ao) in a patient with HCM. The mean LAP is elevated to 35 mm Hg. There is a 74-mm Hg gradient across the LVOT. Top right, Transitral velocity curve of pulsed-wave Doppler at the tip of the mitral valve leaflets as they open into the left atrium. The initial early velocity (E) of 84 cm/s is shown. Bottom left, TDI from the medial annulus. The early diastolic velocity (medial e') is 4.2 cm/s. The ratio of transmitral velocities to Doppler tissue velocity (E-e' ratio) is 20. Bottom right, TDI from the lateral annulus. The early diastolic velocity (lateral e') is 5.6 cm/s. The ratio of transmitral velocities to Doppler tissue velocity (E-e' ratio) is 15.
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Simultaneous Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±13</td>
<td>56±13</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>49 (49)</td>
<td>23 (55)</td>
</tr>
<tr>
<td>NYHA class III or IV, n (%)</td>
<td>82 (82)</td>
<td>38 (90)</td>
</tr>
<tr>
<td>Presyncope or syncope, n (%)</td>
<td>52 (52)</td>
<td>19 (45)</td>
</tr>
<tr>
<td>History of atrial fibrillation, n (%)</td>
<td>17 (17)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>12 (12)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Family history of HCM, n (%)</td>
<td>23 (23)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Family history of SCD, n (%)</td>
<td>10 (10)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Maximum ventricular wall thickness, mm</td>
<td>20.0±5.5</td>
<td>18.9±4.1</td>
</tr>
<tr>
<td>End-diastolic diameter, mm</td>
<td>46.0±5.6</td>
<td>46.2±5.6</td>
</tr>
<tr>
<td>Left atrial volume index, cm³/m²</td>
<td>48±18</td>
<td>52±18</td>
</tr>
<tr>
<td>Resting echo LVOT gradient, mm Hg</td>
<td>52.9±47.2</td>
<td>44.6±47.9</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>71±7</td>
<td>70±5</td>
</tr>
<tr>
<td>Permanent pacemaker, n (%)</td>
<td>13 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Internal cardioverter-defibrillator, n (%)</td>
<td>7 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Receptor antagonist</td>
<td>88 (88)</td>
<td>38 (90)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>53 (53)</td>
<td>22 (52)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>24 (24)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>8 (8)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>7 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Time between echo and catheterization, d</td>
<td>1.0±0.9</td>
<td>0±0</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD. NYHA indicates New York Heart Association; SCD, sudden cardiac death; ACE, angiotensin-converting enzyme; and ARB, angiotensin-receptor blocker.

performed by Bland-Altman analysis. With the use of the same statistical methodology, separate analysis of the lateral E-e' ratio was performed. In addition, a regression equation derived from previously published data in patients without HCM using the medial e' velocity was studied ([(mean LAP) = 0.5762×[E-e' ratio] + 6.1449]). Statistical significance was set a priori at P<0.05.

Results

Baseline Characteristics

Table 1 lists the clinical characteristics of the study population. The mean population age was 58±13 years. The majority of patients (82%) had moderately severe or severe dyspnea (New York Heart Association class III or IV). Ten percent had moderately severe or severe mitral regurgitation. There were no significant differences in demographic or clinical characteristics between the patients undergoing simultaneous TTE and catheterization studies and the remainder of the population.

Hemodynamic Data

Table 2 shows hemodynamic data acquired during TTE and cardiac catheterization; there were no significant differences between patients who underwent simultaneous studies and those who did not. Overall, directly measured mean LAP was 17.4±8.4 mm Hg, with 68 patients (68%) having LAP >12 mm Hg. LVOT gradients were present at rest (≥30 mm Hg) in 58 patients and after provocation (≥50 mm Hg) in 8 others. LVOT gradients were present at rest (≥30 mm Hg) in 19 patients who underwent simultaneous studies.

Bland-Altman analysis of pre-A LV pressure and mean LAP at cardiac catheterization is shown in Figure 2. The mean difference between pre-A LV pressure and mean LAP was −1.3±4.9 mm Hg (95% confidence limits of agreement, ±9.8 mm Hg). Among patients without moderately severe or severe mitral regurgitation, the mean difference was −0.76±3.5 mm Hg (95% confidence limits of agreement, ±7.0 mm Hg). Among all patients, the pre-A LV pressure was lower than the mean LAP at higher levels of mean LAP. Patients with moderately severe or severe mitral regurgitation had a higher mean LAP and a larger difference between mean LAP and pre-A LV pressure than those patients with less severe mitral regurgitation.

Relation of Medial E-e’ Ratio to Invasive Mean LAP

Mean LAP was directly related to the medial E-e’ ratio in the overall group (r=0.44, P<0.0001) (Figure 3). Mean LAP also was related to medial E-e’ ratio among patients without
moderately severe or severe mitral regurgitation ($r=0.38$, $P<0.0001$). A statistical trend was present in the subgroup of patients undergoing simultaneous TTE and catheterization measurements ($r=0.28$, $P=0.07$).

An ROC curve was constructed to show the sensitivity and specificity of the medial E-e’ ratio for LAP values of $\geq 15$ mm Hg and $\geq 20$ mm Hg for the overall subgroup (Figure 4). The AUC for mean LAP $\geq 15$ mm Hg was 0.74±0.49. For mean LAP $\geq 20$ mm Hg, the AUC was 0.73±0.55. For patients with simultaneous studies, the AUCs for mean LAP $\geq 15$ mm Hg and mean LAP $\geq 20$ mm Hg were 0.65±0.55 and 0.61±0.67, respectively.

**Relation of Invasively and Noninvasively Derived Mean LAP (Medial E-e’ Ratio)**

A Bland-Altman correlation was performed to compare mean LAP measured at catheterization with a calculated LV filling pressure derived from the medial E-e’ ratio with the use of a previously described regression equation7 (Figure 5). The mean difference between the calculated LV filling pressure and measured LAP was $-7.3\pm9.3$ mm Hg (95% confidence limits of agreement, ±18.6 mm Hg). With exclusion of the 10 patients with moderately severe or severe mitral regurgitation, the mean difference was $-7.3\pm8.9$ mm Hg (95% confidence limits of agreement, ±17.8 mm Hg). For patients with simultaneous TTE and catheterization measurements,
the mean difference between the calculated LV filling pressure and measured LAP was $-7.6 \pm 9.8$ mm Hg (95% confidence limits of agreement, $\pm 19.6$ mm Hg). In addition, LV filling pressure was derived from a regression equation that had previously correlated the medial E-e' ratio with LV filling pressure in patients without HCM. With the use of this regression equation, the mean difference between the calculated LV filling pressure and measured LAP was $-0.5 \pm 6.9$ mm Hg (95% confidence limits of agreement, $\pm 13.8$ mm Hg).

**Categorical Medial E-e’ Ratio**

Medial E-e’ ratios were divided into 3 categories (<8, 8 to 15, >15) for comparison with directly measured mean LAP (Figure 6). Only 1 patient was found to have a medial E-e’ ratio of <8. Sixty-three patients (63%) had a medial E-e’ ratio of >15. Among these patients, the mean LAP was >20 mm Hg in 28 patients (44%), whereas 17 patients (27%) had a mean LAP <15 mm Hg.

**Comparison of Medial and Lateral e’**

The lateral e’ was higher than the medial e’ (6.8±2.3 versus 5.3±1.8 cm/s; P<0.001), resulting in lower E-e’ ratios from the lateral annulus (14.3±7.0 versus 19.3±8.5; P=0.02). There was a modest correlation of mean LAP with lateral E-e’ ($r=0.31$, $P=0.05$) but no significant correlation between lateral E-e’ and pre-A LV pressure ($r=0.07$, $P=0.64$). With the use of lateral e’ and a previously published regression equation,7 the mean difference between the measured LAP and calculated LV filling pressure was $-3.1 \pm 9.2$ mm Hg (95% confidence limits of agreement, $\pm 18.4$ mm Hg). The mean difference between the measured pre-A LV pressure and calculated LV filling pressure was $-3.2 \pm 10.0$ mm Hg (95% confidence limits of agreement, $\pm 20.0$ mm Hg). ROC analysis of the lateral E-e’ ratio revealed AUCs for mean LAP $\geq 15$ mm Hg and mean LAP $\geq 20$ mm Hg of 0.73±0.50 and 0.57±0.65, respectively. Among the 14 patients with lateral

E-e’ >15, the pre-A LV pressure was >20 mm Hg in 4 and <15 mm Hg in 5.

**Discussion**

This study compared currently available Doppler-derived diastolic parameters with direct measurements of LAP in patients with HCM, the majority of whom had severe symptoms. There were statistically significant correlations between the Doppler-derived diastolic parameters and invasive measurements. However, the predictive accuracy of the E-e’ ratio for estimation of mean LAP in an individual patient was modest. When the E-e’ ratio and a previously published regression equation for derivation of LV filling pressures were used, the 95% confidence limits of agreement exceeded ±18 mm Hg, which is the difference between normal and markedly elevated filling pressures. These observations were evident among all patients as well as those who underwent simultaneous TTE and catheterization studies, indicating that the end result of the complex pathophysiological process of diastolic filling in patients with HCM cannot be assessed reliably by currently used Doppler parameters.

The clinical utility of the E-e’ ratio for assessment of mean LAP in an individual patient can be seen from the ROC curve depicted in Figure 4. Transmural flow velocities depict the relative pressures between the left atrium and the LV and are dependent on LAP, ventricular relaxation, and ventricular suction of the mitral annulus. As such, they provide an overall measure of the rate of ventricular relaxation and suction. Prior studies from our laboratory and others have found clinically useful E-e’ ratio cutoff values: An E-e’ ratio <8 is indicative of normal filling pressures, whereas an E-e’ ratio >15 is indicative of markedly elevated filling pressures.4 However, these same categorical criteria cannot be applied to HCM patients (Figure 6). In our study, only 1 patient had an E-e’ ratio <8. This finding is consistent with the severe diastolic abnormalities known to occur in symptomatic patients with HCM and limits the utility of Doppler velocities for determination of LAP in these patients. Furthermore, LAP was <15 mm Hg in approximately 25% of patients with an E-e’ ratio >15. This observation illustrates the lack of specificity of a high E-e’ ratio in determining marked elevation of filling pressures. Although the combination of TDI and transmitral velocities has been of clinical utility in determining filling abnormalities in other patient populations,4–9,23–26 it is important to recognize their limitations in patients with HCM.

Diastolic dysfunction is found in virtually all patients with HCM27 and is a critical aspect of the underlying pathophysiology of HCM. Its precise nature and etiology in patients with HCM is complex and may be affected by inactivation-dependent processes (myocardial ischemia, intracellular calcium overload), load-dependent processes (myocardial fibrosis, regional asynchrony, and valve state–dependent ventricular wall tension), and atrial hemodynamics.28 Various methods, including cineangiography, radionuclide angiography, and echocardiography, have been used to evaluate diastolic dysfunction in HCM.27,29–37 In these studies, abnormalities of impaired LV relaxation and reduced myocardial compliance have been consistent features present in the vast
majority of HCM patients and may be independent of degree of LVOT obstruction and extent of hypertrophy.28

In the present investigation, the direct measurement of mean LAP was used for LV filling pressure. Prior studies have used surrogates of mean LAP including pulmonary capillary wedge pressure, pre-A LV pressure, and LVEDP.7,26

As shown in Figure 2, there can be a discrepancy between these surrogates and true mean LAP, depending on the compliance of the LV, the height of the V wave, and the relative contribution from atrial contraction. These discrepancies may become greater at higher levels of true LAP and in patients with hemodynamically significant mitral regurgitation. Physiologically, it is the mean LAP that is reflected back into the pulmonary circulation, and this parameter therefore is of greatest importance when the clinical effect of diastolic dysfunction is assessed. Nevertheless, in analyses that utilized pre-A LV pressure, the present study found similar limitations of Doppler parameters in this population of HCM patients.

Prior studies have shown a stronger correlation of filling pressures and Doppler parameters in patients with HCM using the E-e’ ratio from the lateral annulus. In our institution, we have routinely used the TDI from the medial annulus to assess filling pressures on the basis of the higher reliability and accuracy compared with the lateral annulus found in our prior studies.24 Because patients with HCM may have dyssynchronous contraction, we prospectively measured the lateral annulus TDI in patients undergoing simultaneous catheterization and compared findings with both pre-A LV pressure and mean LAP. The 95% confidence limits of agreement were large (±18 mm Hg), with ROC curves similar to those obtained when the medial annulus was used. Thus, precise determination of filling pressure in any individual patient cannot be made whether the medial or lateral annulus is used.

Limitations

The major limitation of this study is the fact that not all echocardiographic studies were performed simultaneously with cardiac catheterization. Loading conditions between an echocardiographic examination and a catheterization performed at a different time may vary and affect the results of a study examining noninvasive evaluation of LV filling pressure. Data are thus presented for the overall population (n=100) as well as for the simultaneous subgroup (n=42). In the present investigation, there was little difference in the results of the subgroup who had simultaneous measurement of Doppler and invasive data versus the entire study group. In addition, the finding that Doppler parameters do not correlate well with invasive measures of mean LAP at any time, irrespective of the possible change in loading conditions, is of clinical relevance for the evaluation and management of patients with HCM. The clinical implication is that an E-e’ ratio performed at a specific time does not rule in or rule out an elevated filling pressure as the cause of symptoms in a patient.

The majority of patients were severely symptomatic, and thus this population may not represent the full spectrum of patients presenting with HCM. There was a low Doppler tissue e’ velocity in the population studied, and only 1 patient had a “normal” E-e’ ratio of <8. However, it has been recognized that patients with HCM, even if asymptomatic, do not have normal annular velocities38 because abnormalities of myocardial relaxation inherent in these patients will lower the e’ tissue velocity. Similarly, in an analysis of >2000 echocardiograms performed in outpatients presenting to our HCM clinic, an E-e’ ratio of <8 was present in <7% of all patients, whereas an E-e’ ratio >15 was present in >45%. Thus, the distribution of E-e’ in this study is similar to that of a large outpatient group of patients presenting with HCM.

Conclusions

Although there is an overall correlation between the E-e’ ratio and invasively derived LAP, LV filling pressures cannot be derived accurately with the use of the E-e’ ratio for an individual patient with symptomatic HCM. To accurately assess the diastolic filling properties of patients with HCM, further analysis of measures such as color M-mode echocardiography, left atrial volume, pulmonary venous pressure, and newer myocardial function parameters, including strain and torsion, is warranted.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Doppler echocardiography has been increasingly used for the noninvasive estimation of ventricular filling pressures. However, relatively few data exist on the utility of these indices in patients with hypertrophic cardiomyopathy (HCM). The present study examined the relation of currently available Doppler parameters to invasively derived left ventricular filling pressures in HCM, including direct measurement of left atrial pressure. One hundred symptomatic HCM patients underwent Doppler assessment and cardiac catheterization within 48 hours, including 42 patients who had simultaneous studies. Mean left atrial pressure was directly related to the mediastinal E’/e’ ratio (r=0.44, P<0.0001). However, significant scatter was present, and the confidence limits of agreement were ±18.6 mm Hg, which spans the difference between normal and markedly elevated filling pressures. Few patients with HCM had “normal” E/e’ ratios, and high E/e’ ratios lacked specificity in identifying severe elevation of left atrial pressure. Thus, although there is a relation between Doppler parameters and invasively measured ventricular filling pressures, precise characterization of these pressures in an individual HCM patient cannot be determined solely with the use of these noninvasive methods.
Evaluation of Left Ventricular Filling Pressures by Doppler Echocardiography in Patients With Hypertrophic Cardiomyopathy: Correlation With Direct Left Atrial Pressure Measurement at Cardiac Catheterization

Jeffrey B. Geske, Paul Sorajja, Rick A. Nishimura and Steve R. Ommen

_Circulation_. 2007;116:2702-2708; originally published online November 19, 2007;
doi: 10.1161/CIRCULATIONAHA.107.698985
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/116/23/2702

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/