Tissue Doppler Imaging Is Superior to Strain Rate Imaging and Postsystolic Shortening on the Prediction of Reverse Remodeling in Both Ischemic and Nonischemic Heart Failure After Cardiac Resynchronization Therapy

Cheuk-Man Yu, MD, FRCP; Jeffrey Wing-Hong Fung, FHKAM; Qing Zhang, MM; Chi-Kin Chan, FHKAM; Yat-Sun Chan, FHKAM; Hong Lin, MM; Leo C.C. Kum, MRCP; Shun-Ling Kong, MN; Yan Zhang, BM; John E. Sanderson, FRCP

Background—A number of noninvasive techniques have been used to predict the effectiveness of cardiac resynchronization therapy (CRT) in heart failure patients, in particular left ventricular (LV) reverse remodeling. This study compared the relative predictive values of tissue Doppler imaging (TDI) and strain-rate imaging (SRI) parameters for LV reverse remodeling in patients who received CRT and examined for potential differences in ischemic (n=22) and nonischemic (n=32) heart failure.

Methods and Results—TDI and SRI were performed at baseline and 3-month follow-up. Eighteen parameters of intraventricular and interventricular asynchrony based on the time to peak myocardial contraction (Ts) and time to peak strain rate (Tsr) were compared, along with postsystolic shortening (PSS). Reverse remodeling with reduction of LV end-diastolic and end-systolic volumes and gain in ejection fraction (all P<0.001) was observed in the whole study population. The standard deviation of Ts of 12 LV segments (Ts-SD) is the most powerful predictor of reverse remodeling in both the ischemic (r=-0.65, P<0.001) and nonischemic (r=-0.79, P<0.001) groups. The PSS of 12 LV segments was a good predictor only for the nonischemic (r=-0.64, P<0.001) but not the ischemic (r=0.32, P=NS) group. However, parameters of SRI and interventricular asynchrony failed to predict reverse remodeling. By multiple regression analysis, independent parameters included Ts-SD in both groups (P<0.005) and PSS of 12 LV segments in the nonischemic group (P=0.03). The area of the receiver operating characteristic curve was largest for Ts-SD (0.94; CI=0.88 to 1.00).

Conclusions—Ts-SD is the most powerful predictor of LV reverse remodeling and was consistently useful for ischemic and nonischemic heart failure. However, PSS is useful only for nonischemic pathogenesis, whereas the role of SRI parameters was not supported by the present study. (Circulation. 2004;110:66-73.)

Key Words: heart failure ■ remodeling ■ pacing ■ echocardiography

Cardiac resynchronization therapy (CRT) has been recommended for patients with advanced chronic heart failure with prolonged QRS complexes. Clinical data have suggested the beneficial role of CRT on symptoms, functional capacity, and left ventricular (LV) reverse remodeling.1-4 In fact, LV reverse remodeling is an objective end point that is thought to contribute to the symptomatic benefits of CRT5 and may herald improved long-term survival.6-8 However, approximately one third of patients do not respond to the therapy clinically or lack reverse remodeling.2,5,9 This might be explained by the fact that direct assessment of systolic asynchrony rather than QRS duration is the key for selecting appropriate patients for CRT and predicting a favorable response.5,10 Echocardiography has been the cornerstone for serial assessment of systolic asynchrony, among which tissue Doppler imaging (TDI) has been most widely used.5,10-11 The main quantitative parameters derived from TDI measured the difference or variation in time to peak regional contraction between 2 or more LV segments,4,5,12,13 the presence of postsystolic shortening (PSS),10 and possibly strain-rate imaging (SRI). Some of these parameters have been suggested to be useful to predict reverse remodeling.5,9,10 In addition, the pattern of systolic asynchrony may be different between ischemic and nonischemic causes of heart failure.10 This may affect the predictive value of the echocardiographic tool chosen. Therefore, the aims of the study were to compare the
relative predictive values of TDI-, PSS-, and SRI-derived parameters on the prediction of LV reverse remodeling and to explore whether there is any difference in such predictive value between ischemic and nonischemic heart failure after CRT.

Methods

Patients
Fifty-four heart failure patients (mean age, 65±11 years; 36 male) who received CRT and were followed up for at least 3 months were analyzed. Inclusion criteria included severe symptomatic heart failure despite optimal pharmacological therapy. Patients were in New York Heart Association (NYHA) class III (n=42) or IV (n=12) heart failure and had evidence of LV systolic dysfunction with an ejection fraction <40% and a QRS duration >120 ms in the form of bundle-branch block or intraventricular conduction delay. The causes of heart failure were ischemic in 22 patients (41%) and nonischemic in 32 (59%). Medications included diuretics in all patients, ACE inhibitors or angiotensin receptor blockers in 97%, β-blockers in 76%, spironolactone in 37%, and digoxin in 20%. Serial echocardiography with TDI and SRI was performed before and 3 months after CRT. The study protocol was approved by the Ethics Committee, and written informed consents were obtained from all the patients.

Biventricular Device Implantation
Biventricular devices were implanted as previously described.4-6 The LV pacing lead was inserted into either the lateral or posterolateral cardiac vein. Thirty-nine patients received an Attain system (model 2187, model 4189, model 4191 [side-wire lead], or model 4193 [over-the-wire]) (Medtronic Inc), and 15 received the Easitrak over-the-wire lead (model 4512, Guidant Inc). Apart from 4 patients who received biventricular cardiac defibrillators (InSync ICD or Contak CD), all the others received biventricular pacemakers (InSync, InSync III, or Contak TR). The atrioventricular interval was optimized by Ritter’s method with a mean value of 99.5±24.8 ms.

Echocardiography
Standard echocardiography, including Doppler studies, was performed (System 5 or Vivid 5, Vingmed-General Electric). The LV volumes and ejection fraction were assessed by biplane Simpson’s method with a mean value of 99.5

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nonresponders (n=23)</th>
<th>Responders (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65±13</td>
<td>66±10</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>15/8</td>
<td>21/10</td>
<td></td>
</tr>
<tr>
<td>Causes of heart failure, ischemic/nonischemic</td>
<td>9/14</td>
<td>13/18</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1±0.5</td>
<td>3.1±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>147±25</td>
<td>155±33</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic volume, cm³</td>
<td>203±78</td>
<td>184±76</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic volume, cm³</td>
<td>156±79</td>
<td>142±73</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic sphericity index</td>
<td>1.68±0.25</td>
<td>1.77±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>24.5±10.0</td>
<td>25.3±9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>2.7±1.1</td>
<td>2.6±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral regurgitation, % left atrial area</td>
<td>37±21</td>
<td>30±19</td>
<td>NS</td>
</tr>
<tr>
<td>LV filling time, ms</td>
<td>353±104</td>
<td>382±106</td>
<td>NS</td>
</tr>
<tr>
<td>+dp/dt, mm Hg/s</td>
<td>581±127</td>
<td>610±206</td>
<td>NS</td>
</tr>
</tbody>
</table>
TABLE 2. Correlation Analysis Between the Change in LV End-Systolic Volume and Parameters of Systolic Asynchrony by Echocardiography for All Patients As Well As Patients With Ischemic and Nonischemic Heart Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>ROC Curve</th>
<th>Ischemic Group</th>
<th>Nonischemic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ts-SD</td>
<td>r: -0.74</td>
<td>p: &lt;0.001</td>
<td>r: 0.94</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-12</td>
<td>r: -0.60</td>
<td>p: &lt;0.001</td>
<td>r: 0.88</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-6-basal</td>
<td>r: -0.60</td>
<td>p: &lt;0.001</td>
<td>r: 0.80</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-med-free</td>
<td>r: -0.46</td>
<td>p: &lt;0.001</td>
<td>r: 0.79</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-basal-med-free</td>
<td>r: -0.46</td>
<td>p: &lt;0.001</td>
<td>r: 0.79</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-sep-lat</td>
<td>r: -0.46</td>
<td>p: &lt;0.001</td>
<td>r: 0.80</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td>Ts-sep-post</td>
<td>r: -0.45</td>
<td>p: &lt;0.001</td>
<td>r: 0.74</td>
<td>p: 0.008</td>
</tr>
<tr>
<td>Tsr-SD</td>
<td>r: -0.01</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-12</td>
<td>r: 0.03</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-6-basal</td>
<td>r: -0.03</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-med-free</td>
<td>r: 0.11</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-basal-med-free</td>
<td>r: 0.16</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-sep-lat</td>
<td>r: 0.003</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-sep-post</td>
<td>r: -0.13</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>No. of PSS-12</td>
<td>r: -0.28</td>
<td>p: 0.05</td>
<td>r: 0.57</td>
<td>p: NS</td>
</tr>
<tr>
<td>No. of PSS-6-basal</td>
<td>r: -0.24</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Ts-IVD</td>
<td>r: -0.13</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>Tsr-IVD</td>
<td>r: -0.09</td>
<td>p: NS</td>
<td>r: ...</td>
<td>p: ...</td>
</tr>
<tr>
<td>QRS duration</td>
<td>r: -0.38</td>
<td>p: 0.005</td>
<td>r: 0.69</td>
<td>p: 0.02</td>
</tr>
</tbody>
</table>

The receiver operating characteristics (ROC) for significant parameters are shown. See text for abbreviations.

The parameter that combined the use of TDI and SRI is the number of segments with PSS (or delay longitudinal contraction), i.e., a positive velocity occurred after systole that was greater than the systolic peak during ejection phase, which was confirmed by SRI to be an active movement by the presence of a negative peak strain rate. Two parameters were derived: number of segments with PSS among the 6 basal segments (PSS-6-basal) and number of segments with PSS among the 6 basal and 6 mid LV segments (PSS-12) and number of segments with PSS among the 6 basal segments (PSS-6-basal).

The parameter that combined the use of TDI and SRI is the number of segments with PSS (or delay longitudinal contraction), i.e., a positive velocity occurred after systole that was greater than the systolic peak during ejection phase, which was confirmed by SRI to be an active movement by the presence of a negative peak strain rate. Two parameters were derived: number of segments with PSS among the 6 basal segments (PSS-6-basal) and number of segments with PSS among the 6 basal and 6 mid LV segments (PSS-12) and number of segments with PSS among the 6 basal segments (PSS-6-basal).

The parameter that combined the use of TDI and SRI is the number of segments with PSS (or delay longitudinal contraction), i.e., a positive velocity occurred after systole that was greater than the systolic peak during ejection phase, which was confirmed by SRI to be an active movement by the presence of a negative peak strain rate. Two parameters were derived: number of segments with PSS among the 6 basal segments (PSS-6-basal) and number of segments with PSS among the 6 basal and 6 mid LV segments (PSS-12) and number of segments with PSS among the 6 basal segments (PSS-6-basal).

The parameter that combined the use of TDI and SRI is the number of segments with PSS (or delay longitudinal contraction), i.e., a positive velocity occurred after systole that was greater than the systolic peak during ejection phase, which was confirmed by SRI to be an active movement by the presence of a negative peak strain rate. Two parameters were derived: number of segments with PSS among the 6 basal segments (PSS-6-basal) and number of segments with PSS among the 6 basal and 6 mid LV segments (PSS-12) and number of segments with PSS among the 6 basal segments (PSS-6-basal).

Statistics

For the comparison of parametric variables before and after CRT, paired-sample t test was used. The comparison of clinical and echocardiographic parameters between ischemic and nonischemic groups was performed by unpaired t test or Pearson χ² test where appropriate. Correlation analysis was used to compare the relationship between parameters of systolic asynchrony and the change of LV end-systolic volume after pacing in a univariate model, followed by multivariate analysis in a stepwise multiple regression model. Receiver operating characteristics (ROC) were analyzed for TDI and PSS parameters. All data were expressed as mean±SD. A probability value of P<0.05 was considered statistically significant.

Results

LV Reverse Remodeling and Cardiac Function

At the end of 3 months, reverse remodeling was achieved, with significant reduction of LV end-diastolic (193±81 versus 164±79 cm³, P<0.001) and end-systolic (148±75 versus 114±67 cm³, P<0.001) volumes. The LV ejection fraction was increased (24.9±9.6% versus 32.9±10.9%, P<0.001). There was significant increase in LV end-diastolic (1.58±0.17 versus 1.73±0.28, P<0.001) and end-systolic (1.74±0.22 versus 1.93±0.32, P<0.001) volumes. The LV filling time was increased (370±108 versus 442±117 ms, P=0.006).

Successful LV reverse remodeling was defined as a reduction of LV end-systolic volume (ΔLVVs) of >15%,5,9,20 which was observed in 31 patients (57%) after CRT for 3 months. The others were regarded as nonresponders who had
a relatively stable ΔLVVs (between −15% and +15%) in 19 patients (35%) or the ΔLVVs was further enlarged >15% in 4 patients (8%). There was no difference in baseline clinical and echocardiographic parameters between responders and nonresponders of reverse remodeling (Table 1). However, improvement of ejection fraction was observed only in responders (25.3±9.5% versus 38.0±8.8%, P=0.001) but not the nonresponders (24.5±10.0% versus 26.6±10.1%, P=NS).

Comparison of TDI, PSS, and SRI Parameters on the Prediction of Reverse Remodeling

As shown in Table 2, all the TDI parameters significantly predicted LV reverse remodeling. Among them, Ts-SD had the strongest predictive value (r=−0.74, P<0.001). A good correlation was also observed when the 6 basal LV segments or all the LV segments (both r=−0.60, P<0.001) were included into the model (Figure 1). The predictive values by other TDI parameters were significant but lower. The PSS and SRI parameters were unable to predict reverse remodeling (Figure 1). The parameters of interventricular asynchrony also failed to predict reverse remodeling. Furthermore, only responders of reverse remodeling showed significant improvement of most TDI parameters, which was worsening in the nonresponders. On stepwise multivariate regression analysis in which the significant parameters were entered into the statistical model, Ts-SD remained the only independent predictor of reverse remodeling response (β=−1.38; CI, −1.79 to −0.97). Other TDI parameters, including PSS and QRS duration, were unable to predict reverse remodeling.

The ROC for parameters with significant correlation with reverse remodeling in the univariate model are shown in Table 2. The area under the curve was largest for Ts-SD (0.94, P<0.001) and was significant for all the other TDI parameters (Figure 2). On the basis of the data on the ROC curve, we concluded that a Ts-SD value of 31.4 ms has a sensitivity of 96% and a specificity of 78% to predict significant reverse remodeling.

Predictive Values of TDI, PSS, and SRI for Reverse Remodeling in Ischemic and Nonischemic Heart Failure

The baseline clinical and echocardiographic features were similar between ischemic and nonischemic groups (Table 3). The degree of pre pacing systolic asynchrony, as shown by Ts-SD and PSS-12, was similar between the 2 groups. Three months after CRT, the reduction of LV volume and gain in ejection fraction were also comparable between the 2 groups. In the ischemic group, 13 of 22 patients (59%) had significant reverse remodeling, and this proportion was comparable to the nonischemic group (18 of 32 patients [56%]; χ²=0.28, P=NS).

In the ischemic group, the predictive values of TDI parameters were in general lower than in patients with
nons ischemic pathogenesis (Table 2 and Figures 1 and 3). In ischemic patients, the best predictor was Ts-SD \( (r = -0.65, P<0.001) \). However, this was decreased precipitously for other TDI parameters, especially Ts-12 and Ts-6-basal \( (r = -0.46 \text{ to } -0.43) \). The parameters by PSS, SRI, and interventricular delay were unable to predict reverse remodeling. In the stepwise multivariate analysis model, Ts-SD was the only independent predictor of reverse remodeling \( ( \beta = -1.37; \text{CI}, -2.22 \text{ to } -0.53; P=0.003) \).

In the nonischemic group, there were 3 TDI parameters that correlated closely with reverse remodeling: Ts-SD was an excellent predictor \( (r = -0.79, P<0.001) \), followed by Ts-12 \( (r = -0.72, P<0.001) \) and Ts-6-basal \( (r = -0.69, P<0.001) \). Interestingly, PSS-12 and PSS-6-basal in the nonischemic group is a reasonably reliable predictor of reverse remodeling \( (r = -0.64 \text{ to } 0.66, \text{both } P<0.001) \). None of the parameters of SRI or interventricular delay predicted reverse remodeling. By stepwise multivariate analysis model, the 2 independent predictors of reverse remodeling were Ts-SD \( (\beta = -1.09; \text{CI}, -1.59 \text{ to } -0.59; P<0.001) \) and PSS-12 \( (\beta = -2.90; \text{CI}, -5.43 \text{ to } -0.38; P=0.03) \).

**Discussion**

**TDI, PSS, SRI, and Reverse Remodeling**

LV reverse remodeling after CRT illustrates the improvement of systolic function and reduction of LV volume that reflects less adverse wall stress. It is probably a combination of improvement in intraventricular synchronicity, \(^4\) hemodynamics, \(^20,21\) atrioventricular synchronicity, \(^22\) interventricular synchronicity, \(^4,6\) and mitral regurgitation. \(^4,6\) Reverse remodeling response was consistently observed, \(^5,6,9,20\) which was thought to contribute to the beneficial effect on symptoms and may herald the improvement of long-term survival. \(^5,8\)

Clinical and volumetric nonresponders to CRT are consistently observed in approximately one third of patients. \(^2,5,9\) Recent efforts were envisaged to search for echocardiographic predictors of response, in which TDI plays a vital role. \(^4,10-12\) An early study observed that Ts-SD, the systolic
asynchrony index, was a powerful predictor of LV reverse remodeling and was able to identify responders. Studies also observed that volumetric responders were associated with clinical improvements. The technique of TDI was also combined with SRI to search for PSS, or delayed longitudinal contraction. The presence of PSS in the basal LV segments was found to correlate with the gain in ejection fraction in 25 patients receiving CRT. In that study, ejection fraction (but not volumetric data) was used as an indicator of reverse remodeling. The septoposterior wall by M-mode measurement was observed to predict reverse remodeling in 20 patients, of whom the majority (n = 16) had a nonischemic pathogenesis. Very recently, the assessment of strain has also been suggested to be useful to assess mechanical events in the ventricle. The present study is the largest prospective study that used TDI, PSS, and SRI to assess cardiac intraventricular and interventricular asynchrony for patients receiving CRT and in a balanced number of patients with ischemic and nonischemic causes. The results demonstrated that TDI parameters closely predict LV reverse remodeling and that Ts-SD (the “asynchrony index”) is the single best predictor. This parameter encompasses information of all the 12 LV segments and reflects systolic asynchrony even if the pattern is more heterogeneous. Furthermore, the more segments analyzed, the higher the predictive value.

In this study, PSS is a very weak predictor of reverse remodeling. The PSS actually described a contractile response observed during early diastole after closure of the aortic valve. Therefore, it is a semiquantitative and indirect marker of systolic asynchrony. Furthermore, occurrence of PSS has been described in normal subjects who had no evidence of cardiac disease. Also, none of the SRI parameters predict reverse remodeling. Tsr reflects the time to peak regional deformation by contractile force and theoretically will be affected by asynchronous contraction but not affected by translational movement. However, such benefit may be offset by the relatively large interobserver and intraobserver variability (at least >16%).

Role of TDI, PSS, and SRI in Ischemic and Nonischemic Heart Failure

In this study, the asynchrony index, Ts-SD, is the strongest independent predictor of LV reverse remodeling for both groups. Interestingly, the predictive values of all the TDI parameters were consistently higher in the nonischemic than the ischemic group. The discrepancy of predictive values with different causes of heart failure may be related to the more heterogeneous pattern of systolic asynchrony in patients with an ischemic pathogenesis. Unlike patients with nonischemic pathogenesis of heart failure, in whom there is a dominant pattern of relative mechanical delay between the septal and free wall regions, systolic asynchrony in ischemic cardiomyopathy may occur in any region of the LV, depending on the vascular territory of ischemia or infarction. As a result, placement of the LV lead in the lateral or posterolateral vein of the coronary sinus in these patients may not be optimal if delay is not at the free wall region. Another interesting observation is that the predictive value of PSS was good only for the nonischemic group. In the ischemic group, PSS may not be a marker of systolic asynchrony but may represent myocardial ischemia or viability. In these situations, CRT may not have altered the occurrence of PSS. We suggest that evaluation of systolic asynchrony by PSS also needs to consider the pathogenesis of heart failure.

Limitations of the Study

The study was conducted by relatively dated echocardiographic instruments that were acquired a few years ago.
Although the current state-of-the-art machine may not significantly enhance the image quality of TDI, the better hardware and software equipment may improve the signal-to-noise ratio of SRI and its predictive value. Mitral regurgitation was assessed only by the change in jet area relative to left atrial area. The use of more complex methods, such as the proximal isovelocity surface area method, is preferable for accurate quantitative assessment of its severity.

Conclusions
As an important and objective marker of response to CRT, LV reverse remodeling occurs only in the majority of patients, not in all, after CRT. Direct assessment of systolic
asynchrony by Ts-SD provides strong and independent predictive value of reverse remodeling of both ischemic and nonischemic causes. The semiquantitative evaluation of PSS-12 is potentially useful for nonischemic but not ischemic patients.

References
Tissue Doppler Imaging Is Superior to Strain Rate Imaging and Postsystolic Shortening on the Prediction of Reverse Remodeling in Both Ischemic and Nonischemic Heart Failure After Cardiac Resynchronization Therapy
Cheuk-Man Yu, Jeffrey Wing-Hong Fung, Qing Zhang, Chi-Kin Chan, Yat-Sun Chan, Hong Lin, Leo C.C. Kum, Shun-Ling Kong, Yan Zhang and John E. Sanderson

Circulation. 2004;110:66-73; originally published online June 14, 2004; doi: 10.1161/01.CIR.0000133276.45198.A5
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/110/1/66

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/