Mechanical Remodeling of the Left Atrium After Loss of Atrioventricular Synchrony
A Long-Term Study in Humans

Paul B. Sparks, MBBS, PhD; Harry G. Mond, MD; Jitendra K. Vohra, MD; Anthony G. Yapanis, MBBS; Leeanne E. Grigg, MBBS; Jonathan M. Kalman, MBBS, PhD

Background—Tachycardia-mediated mechanical remodeling of the atrium is considered central to the pathogenesis of thromboembolism associated with chronic atrial fibrillation. Whether atrial mechanical remodeling also occurs in response to atrial stretch induced by chronic asynchronous ventricular pacing in patients with permanent pacemakers is unknown.

Methods and Results—The study design was a prospective randomized comparison between 21 patients paced chronically in the VVI mode and 11 patients paced chronically in the DDD mode for 3 months. Left atrial appendage (LAA) function and the presence of spontaneous echo contrast (SEC) were determined with transesophageal echocardiography (TEE) within 24 hours of pacemaker implantation and after 3 months. The VVI patients were then programmed to DDD and underwent a third TEE after DDD pacing for an additional 3 months. After chronic VVI pacing, LAA velocity decreased from $82.4\pm29.0$ to $42.1\pm25.4$ cm/s ($P<0.01$), LAA fractional area change decreased from $74.9\pm17.2\%$ to $49.8\pm22.0\%$ ($P<0.01$), and 4 patients (19%) developed left atrial SEC ($P<0.05$). With the reestablishment of chronic AV synchrony, LAA velocity increased to $61.6\pm18.5$ cm/s ($P<0.01$), LAA fractional area change increased to $76.4\pm18.1\%$ ($P<0.01$), and SEC resolved. In the 11 patients undergoing chronic DDD pacing, no significant changes in LAA velocity (baseline, $86.0\pm28.8$ cm/s versus 3 months, $79.6\pm14.9$ cm/s) or LAA fractional area change (baseline, $76.2\pm19.4\%$ versus $72.5\pm15.7\%$) were demonstrated, and SEC did not develop.

Conclusions—Chronic loss of AV synchrony induced by VVI pacing is associated with mechanical remodeling of the left atrium, which may reverse after the reestablishment of AV synchrony with DDD pacing. This process may be partly responsible for the higher incidence of thromboembolism observed in patients undergoing VVI pacing compared with AV sequential pacing. (Circulation. 1999;100:1714-1721.)

Key Words: atrium ■ pacemakers ■ remodeling ■ stroke ■ stunning, myocardial

Experimental evidence suggests that atrial fibrillation (AF) leads to a tachycardia-mediated atrial cardiomyopathy, resulting in not only electrophysiological but also mechanical remodeling of the atria.1–6 The importance of atrial mechanical remodeling has been demonstrated in echocardiographic studies that have linked this phenomenon with embolic stroke. These studies demonstrate that sustained AF leads to left atrial (LA) mechanical dysfunction characterized by progressive reduction in left atrial appendage (LAA) velocities, the development of LA spontaneous echo contrast (LASEC), and the formation of thrombus.7–11 Whether atrial mechanical remodeling occurs in other clinical situations has been less well characterized.

An emerging body of evidence demonstrates that chronic asynchronous ventricular (VVI) pacing is associated with an increased incidence of thromboembolic events.12–14 However, the mechanisms underlying this observation are unknown. We hypothesized that chronic VVI pacing would be associated with atrial mechanical remodeling, providing a potential explanation for the increase in thromboembolic events.

Serial transesophageal echocardiography (TEE) was used to determine the atrial mechanical consequences of chronic loss of atrioventricular (AV) synchrony in patients with pacemakers implanted for AV block or sinus bradycardia. The study was a prospective randomized comparison between patients paced in the VVI versus dual-chamber sequential...
suspected because of intolerance to the loss of AV synchrony. At baseline, 23 patients were randomized to VVI pacing for 3 months, and 11 patients received DDD pacing. The development of thromboembolism, AF, or pacemaker syndrome associated with VVI pacing excluded patients from further study, because immediate reprogramming to DDD pacing was instituted.

Three Months After Pacemaker Implantation

Patients returned for pacemaker interrogation, TTE, and TEE as detailed below. For patients randomized to chronic VVI pacing, TEE parameters were initially assessed in the VVI mode, then were reassessed 15 minutes after reprogramming to DDD mode. For patients randomized to DDD pacing, TEE was performed in the DDD mode only. After the TEE, patients originally programmed to chronic pacing in the VVI mode underwent reprogramming to the DDD mode; patients originally programmed to DDD remained in the DDD mode and were not studied further.

Six Months After Pacemaker Implantation

Patients who had been reprogrammed to DDD pacing (from VVI) at 3 months returned for a third TEE, TTE, and pacemaker interrogation. All echocardiographic parameters were assessed in DDD pacing.

Echocardiographic Analysis

Patients underwent TTE with commercially available 2.5- to 3.5-MHz ultrasound transducers connected to a Hewlett-Packard Sonos 2500 ultrasound system. M-mode dimensions of LA and left ventricular end-systolic and end-diastolic diameters from the left parasternal long-axis view were recorded during DDD pacing. The intercostal space from which LA dimensions were assessed was recorded to standardize imaging between successive studies.

A 5-MHz phased-array multiplane probe connected to a Hewlett-Packard Sonos 2500 ultrasound system was used to perform TEE. All images were recorded on half-inch super-VHS tape and analyzed offline. All LAA velocities were assessed with pulsed-wave Doppler, with the sample volume placed 1 cm into the mouth of the LAA. Mean maximum velocities were obtained by scanning the appendage from 0° to 180° and averaging over 20 consecutive cardiac cycles. The resultant angle was used for all subsequent analyses of LAA function. Maximum and minimum LAA areas were determined by planimetry over 20 consecutive cardiac cycles to calculate fractional area change (FAC) according to the equation $FAC = \frac{\text{maximum area} - \text{minimum area}}{\text{maximum area}}$. LA function was determined by measuring mitral A-wave velocities over 20 consecutive cardiac cycles during DDD pacing by pulsed-wave interrogation of mitral inflow at the level of the mitral leaflet tips.

Spontaneous echocardiographic contrast was defined as the appearance of swirling clouds of echogenicity distinct from white noise artifact. Gain settings were reduced sequentially to distinguish LASEC from noise artifact and maintained for the study duration. Changes in SEC were graded independently by 3 observers and determined by consensus. Analysis was performed offline, and observers were blinded to the other observers’ interpretations and the preceding pacing mode.

Statistical Analysis

All variables are reported as mean±SD. A repeated-measures ANOVA was used to compare continuous variables. Schefé’s F test was used for multiple comparisons. The χ² or McNemar test was used to compare categorical variables. Statistical significance was established at $P<0.05$.

Results

Patient Characteristics

Details of the 2 groups that completed the first 3 months of pacing are presented in Table 1. No significant differences in baseline variables were present. In particular, LA dimensions,
TABLE 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>VVI</th>
<th>DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Age, y</td>
<td>76.0±8.8</td>
<td>77.4±7.7</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (57)</td>
<td>8 (64)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>4 (19)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>AVB, n (%)</td>
<td>11 (52)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Sinus bradycardia, n (%)</td>
<td>10 (48)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>VAC, n (%)</td>
<td>10 (48)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>LA, cm</td>
<td>3.96±0.56</td>
<td>3.72±0.67</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>5.3±0.4</td>
<td>5.1±0.6</td>
</tr>
<tr>
<td>LVESD, cm</td>
<td>3.4±0.4</td>
<td>3.5±0.3</td>
</tr>
</tbody>
</table>

AVB indicates AV block; VAC, VA conduction; LVEDD, left ventricular end-diastolic diameter; and LVESD, left ventricular end-systolic diameter. P=NS for all.

ventriculoatrial (VA) conduction, and the proportion of patients with AV block and sinus bradycardia were similar in both groups.

Two patients in the VVI group were excluded after baseline evaluation because 3 months of pacing was not completed. One patient developed pacemaker syndrome with peripheral edema after 3 weeks. One patient suffered a middle cerebral artery stroke 1 week before the second TEE. Seven of the 21 patients who completed 3 months of VVI pacing and underwent the second TEE did not return for the third TEE. One patient in this group developed AF 2 days after the second TEE. Six patients withdrew voluntarily from the study after the second TEE.

Pacemaker Telemetry

Nineteen of the 21 patients who completed VVI pacing for 3 months demonstrated 100% ventricular pacing. The remaining 2 patients demonstrated 84% and 90% ventricular pacing, respectively. Of the 14 patients who returned at 6 months, 9 demonstrated atrial sensing/atrial pacing with 100% ventricular pacing. The remaining 5 patients demonstrated atrial sensing/atrial pacing with 50% to 90% ventricular pacing. Ten of the 11 patients randomized to DDD pacing for 3 months demonstrated atrial sensing/atrial pacing with 100% ventricular pacing; the remaining patient demonstrated atrial sensing/atrial pacing with 75% ventricular pacing.

LA Size and Function

Baseline LA diameters were not significantly different between the 2 groups (VVI, 3.96±0.56 cm versus DDD, 3.72±0.67 cm). After VVI pacing for 3 months, mean LA diameter increased from 3.96±0.56 to 4.40±0.35 cm (P<0.01). In these patients, mitral A-wave velocity decreased from 74.1±11.0 to 39.3±9.2 cm/s (P<0.01). After reprogramming and 3 months of chronic DDD pacing, LA diameter decreased to 4.05±0.41 cm (P<0.01) and mitral A-wave velocity increased to 79.0±6.6 cm/s (P<0.01); these values were not significantly different from baseline.

In the group randomized to chronic DDD pacing from baseline, no significant differences in LA diameter (3.72±0.67 versus 3.93±0.22 cm) or A-wave velocity (73.1±14.2 versus 71.7±19.4 cm/s) were observed after 3 months.

LAA Velocities

Baseline

Mean LAA velocity of the 34 patients decreased from 83.6±28.6 cm/s during DDD pacing to 39.1±15.7 cm/s with acute VVI pacing (P<0.0001) (Figure 2). There were no significant differences between LAA velocities during acute VVI pacing in patients undergoing longitudinal study in the VVI mode (38.3±14.7 cm/s) versus the DDD mode (41.0±17.1 cm/s).

During DDD pacing, the LAA velocity profile resembled the biphasic signal that is well described during sinus rhythm (41.0±17.1 cm/s). During VVI pacing, 2 distinct velocity profiles were observed. In the presence of VA conduction, the LAA velocity profile directly followed the paced QRS complex. The signal remained biphasic, with discrete emptying and filling waves coinciding with contraction and relaxation of the LAA as observed with real-time 2D imaging. In the absence of VA conduction, the timing of LAA contraction had no consistent relationship with the paced QRS complex, and the signal oscillated between that of DDD pacing when atrial contraction occurred immediately before the paced ventricular complex and low-amplitude signals resembling those observed in chronic AF (Figure 6).

Three Months

After chronic VVI pacing, LAA velocities measured during VVI pacing decreased from 38.2±14.7 cm/s at baseline to

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 mo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA eV, cm/s</td>
<td>38.2±14.7</td>
<td>23.9±8.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LAA FAC, %</td>
<td>40.8±12.3</td>
<td>29.0±14.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

eV indicates emptying velocity.
23.9±8.7 cm/s at 3 months (*P*<0.0001) (Table 2). In this group, LAA velocities measured during DDD pacing decreased from 82.4±29.0 cm/s at baseline to 42.1±25.4 cm/s at 3 months (*P*<0.01) (Table 3 and Figures 3 and 4). After chronic DDD pacing, no significant differences between LAA velocities at baseline (86.0±28.8 cm/s) and 3 months (79.6±14.9 cm/s) were demonstrated (Table 3 and Figures 3 and 4). Patients with AV block and sinus bradycardia demonstrated similar trends in LAA function after either chronic VVI or DDD pacing (Table 4).

**Six Months**

Fourteen patients (67%) returned for a third TEE at 6 months (3 months after conversion from chronic VVI to chronic DDD pacing). Mean LAA velocity increased to 61.6±18.5 cm/s at 6 months (*P*, 0.01); this value was significantly lower than baseline (82.4±29.0 cm/s, *P*, 0.01) (Figure 3, Table 3). Similar improvements in LAA velocities were evident for patients with AV block and sinus bradycardia after 3 months of DDD pacing. However, patients with sinus bradycardia tended to have lower velocities at 6 months than did those with AV block (Table 4).

**LAA Fractional Area Change**

**Baseline**

LA appendage FAC decreased significantly, from 75.3±17.7% during DDD pacing to 38.3±13.5% during VVI pacing in 34 patients at acute baseline evaluation (*P*<0.0001).

**Three Months**

After chronic VVI pacing, LAA FAC measured during VVI pacing decreased from 40.8±12.3% at baseline to 29.0±14.5% at 3 months (*P*<0.01) (Table 2). In this group, LAA FAC measured during DDD pacing decreased from 74.9±17.2% at baseline to 49.8±22.0% at 3 months (*P*<0.01) (Table 3). After chronic DDD pacing, no significant changes between LAA FAC at baseline (76.2±19.4%) and 3 months (72.5±15.7%) were demonstrated (Figure 5). Patients with AV block and sinus bradycardia demonstrated similar trends in LAA FAC after either chronic VVI or DDD pacing (Table 4).

**LASEC and Thrombus**

No patient had LASEC at baseline in the DDD mode. With acute loss of AV synchrony during VVI pacing at baseline, 8 of the 34 patients (23.5%) developed LASEC (2 dense and 6 light) (*P*, 0.01) (Figure 6). Of the 21 patients completing 3 months of VVI pacing, 4 patients (19.0%) had persistent light LASEC during assessment in the DDD mode, with an associated mean LAA velocity of 28.4±5.8 cm/s. In no
patient was LA thrombus demonstrated. At the 6-month assessment (after reprogramming to chronic DDD pacing for 3 months), SEC had resolved in all patients. No patients paced chronically in the DDD mode developed LASEC ($P<0.05$ versus chronic VVI pacing).

**Discussion**

This study presents new information regarding mechanical remodeling of the atrium in humans after chronic loss of AV synchrony. First, significant LAA dysfunction developed immediately after the loss of AV synchrony associated with VVI pacing compared with DDD pacing. Both LAA velocities and FAC decreased with VVI pacing, and 23.5% of patients developed LASEC. Second, chronic VVI pacing for 3 months produced a further decrease in LAA function and promoted the development of LASEC. Even with reprogramming to DDD mode, significant LAA dysfunction persisted. This phenomenon resembles both the atrial mechanical remodeling that develops with chronic AF and the atrial “stunning” observed after the cardioversion of AF to sinus rhythm.7–10 Third, with the reestablishment of AV synchrony through reprogramming to chronic DDD pacing, LAA dysfunction was demonstrated to be partly reversible. Finally, chronic DDD pacing for 3 months with maintenance of AV synchrony was not associated with atrial mechanical remodeling, and hence these observations are not a manifestation of pacing per se.

Mechanical remodeling of the atria has been described previously in patients with chronic AF and atrial flutter.10,16,17 Progressive dilatation and mechanical dysfunction of the LA and LAA develop, with the magnitude of structural and functional change correlating with arrhythmia chronicity.8 Corroborative experimental evidence also suggests that rapid atrial pacing and AF lead to a tachycardia-mediated atrial

![Figure 4. Effects of chronic pacing on LAA velocities measured during DDD pacing. Top left, Baseline LAA velocity during DDD pacing in a patient randomized to chronic VVI pacing. Bottom left, LAA velocity during DDD pacing after chronic VVI pacing for 3 months. Top right, Baseline LAA velocity during DDD pacing in a patient randomized to chronic DDD pacing. Bottom right, LAA velocity during DDD pacing after chronic DDD pacing for 3 months. Vertical axis, left atrial appendage velocity (cm/s).](image)

**TABLE 4. Comparison of Patients With AV Block and Sinus Bradycardia: LAA Function During DDD Pacing in the VVI/DDD Crossover Group and the DDD Group**

<table>
<thead>
<tr>
<th>LAA FAC, %</th>
<th>VVI/DDD Crossover Group</th>
<th>DDD Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVB</td>
<td>Baseline</td>
<td>3 mo</td>
</tr>
<tr>
<td>70.6±19.6</td>
<td>76.3±19.2†</td>
<td>71.0±26.7</td>
</tr>
<tr>
<td>77.1±15.4</td>
<td>76.6±18.5†</td>
<td>80.6±11.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LAA FAC, %</th>
<th>VVI/DDD Crossover Group</th>
<th>DDD Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBc</td>
<td>Baseline</td>
<td>3 mo</td>
</tr>
<tr>
<td>79.5±25.2</td>
<td>66.7±8.8†</td>
<td>87.2±29.4</td>
</tr>
<tr>
<td>84.8±32.8</td>
<td>56.7±24.7†</td>
<td>85.0±31.0</td>
</tr>
</tbody>
</table>

$eV$ indicates emptying velocity; AVB, AV block; and SBc, sinus bradycardia.

$*P<0.01$ vs baseline, $†P<0.01$ vs 3 months.
cardiomyopathy, resulting in progressive anatomic remodeling of the atria. Structural remodeling of the atria also results from atrial stretch. Animal models of mitral valve fibrosis, tricuspid valve avulsion/pulmonary artery banding, and pacing-induced ventricular failure have demonstrated atrial dilatation.

**Effects of Loss of AV Synchrony on LA Function**

Right ventricular apical pacing with loss of AV synchrony results in altered ventricular activation, ventricular dysfunction, mitral regurgitation, and atrial contraction against closed AV valves, leading to increased atrial pressures and volumes at rest and during exercise. Few prospective studies have examined the consequences of chronic VVI pacing on atrial size and function. Nielsen et al evaluated changes in LA diameter after 5.5 ± 2.4 years of AAI or VVI pacing, with greater increases in LA diameter demonstrated after VVI pacing. Atrial dilatation was independent of AF, retrograde VA conduction, and mitral regurgitation, suggesting that pacing mode alone was responsible for LA dilatation.

Unlike previous studies, we measured LA size and function during DDD pacing, and the acute effects of increased pressure on atrial size from loss of AV synchrony were minimized. Nonetheless, both LA dilatation and LA dysfunction were demonstrated after chronic VVI pacing. Two patients developed possible complications of VVI pacing (AF and stroke), which may relate to LA dysfunction. Atrial dilatation and dysfunction regressed with the reestablishment of AV synchrony, suggesting that LA remodeling may be reversible.

**Figure 5.** Effects of chronic pacing on LAA fractional area change measured during DDD pacing. Left, LAA fractional area change at baseline and after chronic VVI pacing for 3 months followed by DDD pacing and assessment at 6 months. Right, Left atrial appendage fractional area change at baseline and after chronic DDD pacing for 3 months. Vertical axis, LAA fractional area change (%). Horizontal arrows (→) indicate chronic pacing mode in the interval 3-month period; x, individual LAA fractional area change measurements; and ■, mean LAA fractional area change. SD is indicated.

**Figure 6.** TEE images of the LAA velocity profile and 2D images of the LA during acute pacing in the DDD mode and the VVI mode at baseline. Top left, LAA velocity profile during DDD pacing. Bottom left, 2D image of LA and left ventricle (LV) during DDD pacing. Top right, LAA velocity profile during VVI pacing. Bottom right, 2D image of LA and left ventricle with LASEC during VVI pacing. Vertical axis in top panels, LAA velocity (cm/s). LAAeV indicates left atrial appendage velocity (cm/s).
TEE Studies of Cardiac Pacing
One preliminary study demonstrated LAA velocities to be lower during acute VVI pacing than DDD pacing. The present study confirms this finding but also demonstrates that acute loss of AV synchrony is associated with a reduction in LAA FAC and the development of LASEC. The present study prospectively evaluated changes in LAA function after chronic cardiac pacing and demonstrated LAA velocities to decrease in association with a reduction in FAC and the development of SEC. Although atrial thrombus was not demonstrated, it cannot be completely excluded, especially in light of the occurrence of stroke in 1 patient. Our findings are in agreement with previous studies that have shown LAA velocities to be lower and LASEC more frequent with VVI pacing.

After the reestablishment of AV synchrony with chronic DDD pacing, LAA function improved with the disappearance of LASEC, suggesting that the observed atrial remodeling may be reversible. This recovery of atrial mechanical function resembles that observed after cardioversion from AF.

Potential Mechanisms of Atrial Mechanical Remodeling
The cause of atrial mechanical remodeling after VVI pacing is not known. The reduction in atrial contractile function may be analogous to that observed when ventricular myocardium is exposed to volume overload. Chronic volume and pressure overload causes a reduction in myocardial energy production and supply, alteration in contractile proteins, myofibril dropout, the expression of fetal isoforms, and a decrease in myosin calcium ATPase. Similar events could explain the atrial contractile dysfunction observed in the present study. Canine atrial anatomic remodeling secondary to AF is manifested as replacement of sarcomeres by glycogen and atrial cardiomyocyte dedifferentiation with reexpression of embryonic contractile and cytoskeletal proteins. Tissue from dilated human atria demonstrates myofibrillar replacement by clusters of irregular mitochondria, aggregates of dilated sarcoplasmic reticulum, and glycogen. Similar structural changes may explain the atrial remodeling observed with VVI pacing. Stretch-induced intracellular calcium overload might also contribute, given the important role of calcium overload in rate-related atrial mechanical dysfunction.

Limitations
Right heart catheterization was not performed because of the risks of displacing recently implanted pacing leads. Previous studies have confirmed that biatrial pressures increase with VVI pacing, and similar findings are likely to have been observed in the present study. Only LAA function and mitral A-wave velocities were used to characterize atrial remodeling. Given the complex 3D anatomy of the LA, certain regions (nontrabeculated) may be more susceptible to stretch than other regions (trabeculated), and remodeling could occur heterogeneously. Indeed, differential stretch related to degree of trabeculation has been demonstrated in the right atrium, leading to heterogeneous atrial electrical remodeling. Our study did not address changes in right atrial size and function, and whether mechanical remodeling of the right atrium also develops after loss of AV synchrony is unknown.

Conclusions
Chronic loss of AV synchrony with VVI pacing is associated with mechanical remodeling of the atrium. Acute VVI pacing produces an immediate decrease in LAA function with the development of LASEC. Chronic loss of AV synchrony leads to further deterioration in LAA function, which persists in the short term even with resumption of AV synchrony through DDD pacing. Provision of AV synchrony with subsequent chronic DDD pacing leads to an improvement in LAA function. Reversible atrial mechanical remodeling may occur in humans after the chronic loss of AV synchrony, and this suggests a possible mechanism for the increased incidence of stroke in patients undergoing chronic VVI pacing.

Acknowledgment
Dr Sparks is the recipient of a Postgraduate Medical Research Scholarship from the National Heart Foundation of Australia.

References


Mechanical Remodeling of the Left Atrium After Loss of Atrioventricular Synchrony: A Long-Term Study in Humans
Paul B. Sparks, Harry G. Mond, Jitendra K. Vohra, Anthony G. Yapanis, Leeanne E. Grigg and Jonathan M. Kalman

Circulation. 1999;100:1714-1721
doi: 10.1161/01.CIR.100.16.1714

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/100/16/1714

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/