Chronobiological Patterns of Acute Aortic Dissection

Rajendra H. Mehta, MD; Roberto Manfredini, MD; Fauziya Hassan, MD; Udo Sechtem, MD; Eduardo Bossone, MD; Jae K. Oh, MD; Jeanna V. Cooper, MS; Dean E. Smith, PhD; Francesco Portaluppi, MD; Marc Penn, MD; Stuart Hutchison, MD; Christoph A. Nienaber, MD; Eric M. Isselbacher, MD; Kim A. Eagle, MD; on Behalf of the International Registry of Acute Aortic Dissection (IRAD) Investigators

Background—Chronobiological rhythms have been shown to influence the occurrence of a variety of cardiovascular disorders. However, the effects of the time of the day, the day of the week, or monthly/seasonal changes on acute aortic dissection (AAD) have not been well studied.

Methods and Results—Accordingly, we evaluated 957 patients enrolled in the International Registry of Acute Aortic Dissection (IRAD) between 1996 and 2000 (mean age 62±14 years, type A 61%). A χ² test for goodness of fit and partial Fourier analysis were used to evaluate nonuniformity and rhythmicity of AAD during circadian, weekly, and monthly periods. A significantly higher frequency of AAD occurred from 6:00 AM to 12:00 noon compared with other time periods (12:00 noon to 6:00 PM, 6:00 PM to 12:00 midnight, and 12:00 midnight to 6:00 AM; P<0.001 by χ² test). Fourier analysis showed a highly significant circadian variation (P<0.001) with a peak between 8:00 AM and 9:00 AM. Although no significant variation was found for the day of the week, the frequency of AAD was significantly higher during winter (P=0.008 versus other seasons by χ² test). Fourier analysis confirmed this monthly variation with a peak in January (P<0.001). Subgroup analysis identified a significant association for all subgroups with circadian rhythm. However, seasonal/monthly variations were observed only among patients aged <70 years, those with type B AAD, and those without hypertension or diabetes.

Conclusions—Similar to other cardiovascular conditions, AAD exhibits significant circadian and seasonal/monthly variations. Our findings may have important implications for the prevention of AAD by tailoring treatment strategies to ensure maximal benefits during the vulnerable periods. (Circulation. 2002;106:1110-1115.)

Key Words: aorta ■ circadian rhythm ■ seasons

There is considerable evidence indicating that several major adverse cardiovascular events are not randomly distributed over time but demonstrate chronobiological (circadian, weekly, and seasonal/monthly) patterns in their times of occurrence. The cardiovascular conditions shown to be associated with such rhythmic variations include acute myocardial infarction,1–5 sudden death,6 supraventricular tachycardia,7 stable angina,8 silent ischemia,9 cerebrovascular accidents,10 subarachnoid hemorrhage,11 and spontaneous rupture of abdominal aortic aneurysm.12 An increased incidence of these events has been shown to occur early in the morning within the first 3 hours of waking up,1,2,4 in winter,3 and on Monday mornings.3,5 However, the influence of the time of day, the day of the week, and the seasonal or monthly changes on the onset of acute aortic dissection (AAD) has not been well studied in a large cohort of patients.

The present study analyzed patients enrolled in the International Registry of Acute Aortic Dissection (IRAD)13 to examine the chronobiological rhythms of AAD. We hypothesized that similar to other cardiovascular diseases, AAD would demonstrate significant chronobiological patterns.

Methods

Patient Selection
We analyzed all patients with nontraumatic AAD enrolled in IRAD from January 1, 1996, to December 31, 2000 (n=999). Because iatrogenic dissections are not influenced by chronobiological patterns, these patients were excluded from the analysis (Table 1). The institution and structure of IRAD have been described previously.13 All patients were identified prospectively at presentation or retrospectively by searching hospital discharge diagnosis records and/or surgical, pathological, and echocardiographic databases. Diagnosis was based on history and examination and was confirmed by...
imaging studies, by visualization at surgery, and/or by postmortem examination. Type A dissection was defined as any dissection that involved the ascending aorta, whereas type B dissection was defined as one that involved the descending aorta. Acute dissection was defined as presentation within 14 days of the symptom onset.13

Data Collection
Data were collected on a standard questionnaire that included information on patient demographics, history, clinical presentations, imaging study results, and in-hospital management and outcome. Completed data entry forms were forwarded to the IRAD coordinating center at the University of Michigan. Data were scanned electronically into an Access database.

Time, Day, and Month or Season of Symptom Onset
The time of symptom onset of the AAD (defined as the earliest time of symptoms as reported by the patient, relatives, or witnesses) was noted on the data-entry forms. The site coordinators obtained information about time of onset from that documented in the patient’s chart by the physician(s). Alternately, the site coordinators interviewed patients or relatives to gather this information. Precise time of symptom onset (within the hour) was available in 689 (72.0%) of 957 patients (Table 1). These patients were included in the analysis of circadian rhythmicity performed on hourly data after categorization into 24 one-hour increments (eg, onset time between 6:00 AM and 6:59 AM categorized in the 6:00 AM group).7,10 Similarly, we also categorized patients for the analysis of circadian pattern into 4 time periods: 6:00 AM to 11:59 AM, 12:00 noon to 5:59 PM, 6:00 PM to 11:59 PM, and 12:00 midnight to 5:59 AM.

As opposed to the precise hour, the exact date of symptom onset was available for 932 (97.4%) of 957 patients, who were included in the analysis evaluating weekly and seasonal rhythmicity (Table 1). All patients were categorized into seven 1-day-of-the-week periods and twelve 1-month periods. The starting reference point was assumed to be midnight, Sunday, and December 21st for the circadian, weekly, and monthly/seasonal analyses, respectively. For the purpose of seasonal analysis, patients were grouped according to their symptom onset in to 4 groups (winter, December 21st through March 20th; spring, March 21st through June 20th; summer, June 21st through September 20th; and autumn, September 21st through December 20th).7,10,11

Statistical Analysis
The distribution of symptom onset within the 4 time-of-day intervals was tested for uniformity in the overall population and in the various patient subsets by the χ² test for goodness of fit.14 A χ² value large enough to reject the hypothesis implied nonuniformity. We also tested whether the frequency of AAD during the morning time period (6:00 AM to 11:59 AM) was significantly different from the other 3 time periods by using the χ² test. The analysis of circadian rhythmicity was performed on hourly data by applying a partial Fourier series to the time-series data by using Chronolab software on an Apple Macintosh computer.15 With the program, estimates of the amplitude (half of peak to trough of rhythmic change) and acrophase (peak time of rhythmic change) of each harmonic were calculated. As a result of preliminary testing, a Fourier model with 4 harmonics (periods of 24, 12, 8, and 6 hours) was chosen as best fit for our data. The parameters calculated for the overall fit with 4 harmonics were the midline estimated statistic of rhythm (MESOR, the rhythm-adjusted mean over the time period analyzed), amplitude (half the distance between the absolute maximum and minimum of the fitted curve), and the peak and trough times (times of occurrence of absolute maximum and minimum, respectively).

The percentage of rhythm (percentage of overall variability of data about the arithmetic mean attributable to the fitted rhythmic function) and the probability value resulting from the F statistic (used to test the hypothesis of 0 amplitude) were reported in the results as representative parameters of goodness of fit and statistical significance of the fitted function, respectively.

**Figure 1.** Frequency of symptom onset of AAD during the 4 time periods of the day.
The temporal distribution of AAD with weekly and monthly (seasonal) rhythmicity was evaluated by using similar analyses. The nonlinear Fourier analysis of the daily and the monthly data were best fit by a single harmonic with a period of 168 or 8766 hours, respectively. A value of $P<0.05$ was considered significant in all tests. Finally, we evaluated the influence of the time of the day, the day of the week, and the seasonal (monthly) changes on the in-hospital mortality in patients with aortic dissection by use of the $\chi^2$ test.

### Results

#### Characteristics of Study Population

Of 957 patients with AAD in the study, type A AAD and type B AAD were present in 61.2% and 38.8% of the patients, respectively (mean age 62±14 years, 68.2% males). A prior history of hypertension was present in a large number of patients (72.4%), whereas diabetes mellitus (4.6%), Marfan’s syndrome (5.3%), and bicuspid aortic valve (3.6%) occurred in a small minority. Most patients with type A dissection underwent surgical repair (80.9%), whereas the majority of patients with type B dissection were managed medically (73.3%). In-hospital mortality occurred in 24% of patients (31% in type A versus 12% in type B).

#### Circadian Rhythm of AAD

The frequency of onset of AAD was significantly increased during the period from 6:00 AM to noon, when analysis of the data grouped according to four 6-hour intervals was performed ($\chi^2 81.7$, $df 3$, and $P<0.001$ and $\chi^2 54.3$, $df 1$, and $P<0.001$ for comparison of the frequency of symptom onset during the period of 6:00 AM to noon compared with the other three 6-hour periods, respectively; Figure 1). Similarly, nonlinear rhythm analysis (Table 1) identified highly significant ($P<0.001$) circadian variations in the occurrence of AAD in the total population studied, with a morning peak between 8:00 and 9:00 AM and a nocturnal trough between 3:00 and 4:00 AM (Figure 2, Table 2).

Circadian variations in the occurrence of AAD were documented in almost all the subgroups examined (Table 2). Only diabetes was not associated with any significant circadian pattern of AAD ($P=0.32$). The peak timing of onset was delayed by 30 to 60 minutes for women compared with men and for older compared with younger patients (Table 2).

In-hospital mortality was similar among aortic dissections occurring in the 4 time periods ($\chi^2 1.8$, $df 3$, $P=0.61$) as well as between those occurring between 6:00 AM and 12:00 noon compared with the other 3 time periods ($\chi^2 0.8$, $df 1$, $P=0.36$).

#### Weekly, Monthly, and Seasonal Variations in Frequency of AAD

No significant variation was observed in the frequency of AAD on different days of the week in the overall population ($\chi^2 9.1$, $df 6$, $P=NS$) or among various patient subgroups (data not shown). In contrast, a significant seasonal variation occurred in the frequency of aortic dissection, with the highest frequency during winter ($\chi^2 17.5$, $df 3$, $P=0.001$; Figure 3). The winter peak was also significantly greater

### Table 2. Circadian Rhythm Parameters of Fourier Model With 4 Harmonics (Periods of 24, 12, 8, and 6 h) Fitted to Hourly Data of Occurrence of AAD

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MESOR</th>
<th>Amplitude</th>
<th>Peak, AM</th>
<th>Trough, AM</th>
<th>PR, %</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>689</td>
<td>28.71±1.02</td>
<td>19.90±1.44</td>
<td>8.40</td>
<td>3.40</td>
<td>88.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>491</td>
<td>20.46±0.81</td>
<td>16.48±1.15</td>
<td>8.28</td>
<td>3.48</td>
<td>88.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>198</td>
<td>8.25±0.43</td>
<td>5.19±0.61</td>
<td>9.24</td>
<td>1.00</td>
<td>69.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Type A</td>
<td>434</td>
<td>18.08±1.05</td>
<td>13.84±1.49</td>
<td>8.32</td>
<td>2.36</td>
<td>78.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type B</td>
<td>255</td>
<td>10.62±0.62</td>
<td>6.96±0.88</td>
<td>8.52</td>
<td>4.44</td>
<td>69.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Age &lt;70 y</td>
<td>459</td>
<td>19.12±0.74</td>
<td>14.07±1.05</td>
<td>8.32</td>
<td>3.56</td>
<td>87.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>230</td>
<td>9.58±0.61</td>
<td>6.55±0.86</td>
<td>9.04</td>
<td>1.32</td>
<td>68.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>486</td>
<td>20.25±1.03</td>
<td>13.40±1.46</td>
<td>8.44</td>
<td>3.48</td>
<td>76.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Normotensive</td>
<td>191</td>
<td>7.96±0.34</td>
<td>6.72±0.49</td>
<td>8.28</td>
<td>3.24</td>
<td>89.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic</td>
<td>21</td>
<td>0.88±0.19</td>
<td>0.94±0.27</td>
<td>9.20</td>
<td>2.12</td>
<td>40.6</td>
<td>0.323</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>643</td>
<td>26.79±0.86</td>
<td>18.99±1.22</td>
<td>8.36</td>
<td>3.36</td>
<td>90.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Letter n indicates number of cases in each group; PR, percentage of rhythm (percentage of overall variability of data about arithmetic mean attributable to fitted rhythmic function); and $P$, probability value resulting from the F statistic used to test hypothesis of 0 amplitude.
compared with the other 3 seasons ($\chi^2 7.0, \text{df} 1, P=0.008$). Nonlinear Fourier rhythm analysis identified significant ($P=0.022$) monthly (seasonal) variations in the occurrence of AAD in the total population studied, with a peak in the month of January (Figure 4, Table 3). Subgroup analysis identified that the monthly (seasonal) trend was more apparent for women, for those with type B aortic dissection, for younger patients, for patients without a history of hypertension, and for nondiabetic patients, with peak incidence in all these subgroups in the months of January through February (Table 3). Monthly (seasonal) variation was not observed for men, for older patients, or for those with type A aortic dissection, hypertension, or diabetes (Table 3). In-hospital mortality did not differ among aortic dissections occurring in the 4 seasons ($\chi^2 1.2, \text{df} 3, P=0.74$) as well as between those occurring in winter compared with the other 3 seasons ($\chi^2 0.9, \text{df} 1, P=0.33$).

**Figure 3.** Frequency of symptom onset of AAD during different seasons of the year.

**Discussion**

The data from IRAD indicate a strong influence of chronobiological rhythm on the occurrence of AAD. These cyclic changes result in marked circadian periodicity in the occurrence of AAD, with peak frequency in the morning hours. This finding is similar to many prior studies that have reported circadian variability of other cardiovascular conditions.\(^1\)\(^-\)\(^12\) We also demonstrate that the peak incidence of this adverse cardiovascular event occurs during early morning, when people awaken and begin normal activities, identical to the timing of onset of other adverse cardiovascular events.\(^4\)\(^,\)\(^12\) This similarity suggests that common underlying pathophysiological mechanisms may be responsible for the triggering of these cardiovascular events, including aortic dissection. Furthermore, our data identified that the circadian pattern of an early morning peak exists among all subgroups examined (Table 2), suggesting that the association of underlying pathophysiological triggers occur independent of these factors, affecting them equally. Interestingly, women (versus men) and older (versus younger) patients showed a somewhat delayed morning peak in the occurrence of aortic dissection. This might be caused by a later time of awakening from sleep in women and older patients, but this cannot be proven from the present study because we did not collect this information on time of waking in IRAD. The lack of definitive periodicity for cardiovascular events among diabetic patients opposed to nondiabetic patients has previously been reported.\(^16\) Although the present study showed that diabetic patients did not demonstrate circadian variation in the incidence of aortic dissection, this interpretation should be made with caution given the relatively small number of diabetic patients in IRAD ($n=40, 4.3\%$).

Although there was no weekly pattern in the occurrence of aortic dissection, the present study provides evidence that seasonal changes affect the onset of aortic dissection. The highest rate of aortic dissection occurred in winter and in the
TABLE 3. Monthly Rhythmic Parameters of Fourier Model (Single Harmonic With Period of 8766 h) Fitted to Monthly Data of Occurrence of AAD

<table>
<thead>
<tr>
<th>No. of AAD Events, mean ± SEM</th>
<th>n</th>
<th>MESOR</th>
<th>Amplitude</th>
<th>Acrophase</th>
<th>95% Confidence Limits</th>
<th>PR, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>932</td>
<td>77.60 ± 3.00</td>
<td>14.66 ± 4.25</td>
<td>January</td>
<td>January–February</td>
<td>57.0</td>
<td>0.022</td>
</tr>
<tr>
<td>Men</td>
<td>587</td>
<td>53.06 ± 2.89</td>
<td>9.13 ± 4.10</td>
<td>December</td>
<td>NS</td>
<td>35.6</td>
<td>0.138</td>
</tr>
<tr>
<td>Women</td>
<td>295</td>
<td>24.55 ± 1.22</td>
<td>6.71 ± 1.72</td>
<td>February</td>
<td>January–February</td>
<td>62.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Type A</td>
<td>570</td>
<td>47.48 ± 2.60</td>
<td>6.04 ± 3.68</td>
<td>December</td>
<td>NS</td>
<td>23.0</td>
<td>0.308</td>
</tr>
<tr>
<td>Type B</td>
<td>362</td>
<td>30.12 ± 2.07</td>
<td>9.40 ± 2.93</td>
<td>February</td>
<td>January–March</td>
<td>53.5</td>
<td>0.032</td>
</tr>
<tr>
<td>Age &lt;70 y</td>
<td>611</td>
<td>50.86 ± 2.13</td>
<td>11.74 ± 3.02</td>
<td>January</td>
<td>December–February</td>
<td>62.8</td>
<td>0.012</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>321</td>
<td>26.74 ± 1.27</td>
<td>2.91 ± 1.81</td>
<td>January</td>
<td>NS</td>
<td>22.5</td>
<td>0.317</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>655</td>
<td>54.55 ± 2.23</td>
<td>8.73 ± 3.16</td>
<td>January</td>
<td>NS</td>
<td>45.9</td>
<td>0.063</td>
</tr>
<tr>
<td>Normotensive</td>
<td>255</td>
<td>21.22 ± 1.41</td>
<td>6.14 ± 1.99</td>
<td>January</td>
<td>December–March</td>
<td>51.5</td>
<td>0.039</td>
</tr>
<tr>
<td>Diabetic</td>
<td>40</td>
<td>3.34 ± 0.68</td>
<td>0.41 ± 0.96</td>
<td>September</td>
<td>NS</td>
<td>2.0</td>
<td>0.915</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>858</td>
<td>71.43 ± 2.31</td>
<td>14.58 ± 3.27</td>
<td>January</td>
<td>December–February</td>
<td>69.0</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Acrophase indicates month of peak rhythmic change.

month of January, much akin to the winter peak seen for other cardiovascular events. This finding suggests a common link regarding the pathophysiology/triggering of these events. Subgroup analysis suggested that this monthly/seasonal pattern was more evident in patients who were young (aged <70 years), in women, and in normotensive and nondiabetic individuals but not among older patients, men, and hypertensive or diabetic patients, who are otherwise at a high-risk for most cardiovascular events. These data indicate that these clinical factors might have a differential seasonal effect on the pathophysiological mechanism that underlies the development of AAD.

Few prior studies have evaluated the chronobiological patterns of AAD. Gallerani et al19 studied 70 patients with aortic dissection and found a peak occurrence of the aortic tear at 10:00 AM. Manfredini et al20 examined a small number of patients with nontraumatic rupture of the thoracic aorta (n=85) and found a peak in January. Similarly, Sumiyoshi et al21 studied 435 patients with AAD and demonstrated that the highest peak of dissection occurred between the morning hours of 8:00 AM and 11:00 AM and during the months of December, January, and March. However, unlike the present study, they had fewer patients studied at a single institution, did not use nonlinear Fourier analysis, and did not evaluate chronobiological patterns among different subgroups. In contrast, our investigation studied the largest number of patients with AAD to date enrolled in IRAD across the globe. Using nonlinear Fourier analysis, the present study not only confirmed the overall existence of a chronobiological pattern19–21 but also showed that a significant difference in the seasonal pattern exists for AAD among different subgroups of patients. Furthermore, the present study shows for the first time that once aortic tear occurs, the in-hospital mortality is high and is not influenced by the time of the day or the different seasons of occurrence of aortic dissection.

Two potentially synergistic mechanisms may play a role in the occurrence of the chronobiological periodicity. These include the rhythmic variation in the sympathovagal balance and in the hemorheologic properties of circulating blood. Prior investigators have demonstrated a surge in sympathetic activity accompanied by vagal withdrawal in the morning hours, leading to an increase in shear forces secondary to elevation in blood pressure, heart rate, and the rate of pressure change (dP/dt).22 Similarly, the equilibrium between thrombotic and thrombolytic factors changes in the early morning hours, leading to an increase in hypercoagulability (increased platelet aggregability and greater fibrinogen levels and factor VII activity)23,24 and hypofibrinolysis (lower fibrinolytic activity).24 This increases the viscosity of the blood,25 which may, in turn, further contribute to the increased arterial shear forces in the morning caused by a heightened sympathetic tone. Such forces presumably act on the aortic wall, which is inherently weakened by genetic and acquired disorders, causing triggering of AAD during the early morning hours. Similar imbalances of the autonomic nervous system and changes in the hemorheologic properties of blood have been shown to occur with greater magnitude in winter, perhaps accounting for the increased winter rates of aortic dissection.26

The absence of seasonal variability in the aortic dissection rates among men, the elderly, and patients with hypertension or type A dissection is difficult to comprehend if the autonomic nervous system and hemorheologic changes are to be implicated for both circannual and circadian differences in the timing of AAD. It is possible that the daily fluctuation in sympathetic tone and hemostatic properties has a far greater effect than that attributable to seasonal changes. This is supported by our finding that the amplitude of the harmonic curve is greater for the day-to-day variation (19.9) than that for the seasonal fluctuation (14.7) in the incidence of aortic dissection. Compared with women, men are perhaps more resistant to these smaller changes in the underlying sympathetic tone or hemorheologic properties across different seasons, but they may still be susceptible to greater daily fluctuation. One can speculate that the absence of a circannual pattern in the elderly may be related to a greater
autonomic dysfunction in this cohort, resulting in a smaller seasonal than diurnal variation in the sympathetic nervous system activity. Similarly, it is possible that compared with type B dissection, type A dissection may require a higher triggering shear stress, and perhaps the monthly/seasonal change is insufficient to reach such a threshold compared with the larger daily variation. Finally, antihypertensive medications may be sufficient to blunt the smaller seasonal surges in shear stress but may not substantially alter the deleterious effect of the diurnal variation of these forces in hypertensive patients. All these hypotheses will require further confirmation in future studies.

Conclusions of the Study
We conclude that like many other cardiovascular conditions, AAD exhibits a significant circadian and circannual variation in its frequency of occurrence. For patients with an unusually high risk for aortic dissection or for those at risk of an extension of their aortic tear, the present study may have implications for tailoring antihypertensive and β-blocker therapies to ensure maximal benefit during these particularly vulnerable time periods.

References
Chronobiological Patterns of Acute Aortic Dissection
Rajendra H. Mehta, Roberto Manfredini, Fauziya Hassan, Udo Sechtem, Eduardo Bossone, Jae K. Oh, Jeanna V. Cooper, Dean E. Smith, Francesco Portaluppi, Marc Penn, Stuart Hutchison, Christoph A. Nienaber, Eric M. Isselbacher and Kim A. Eagle
on Behalf of the International Registry of Acute Aortic Dissection (IRAD) Investigators

Circulation. 2002;106:1110-1115; originally published online August 12, 2002;
doi: 10.1161/01.CIR.0000027568.39540.4B
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/106/9/1110

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/