The mechanism of disappearance of the physiologic third heart sound with age

FRANS VAN DE WERF, M.D., JEF GEBOERS, Lic.Math., HUGO KESTELoot, M.D., Hilaire de Geest, M.D., AND LAURENTINO BARRIOS, M.D.*

ABSTRACT To study the mechanism of disappearance of the physiologic third heart sound (S₃) with advancing age, combined phonoechocardiographic and phonomechanocardiographic recordings from 165 normal subjects between 6 and 62 years old were quantitatively analyzed. Nearly all individuals under 40 years old had a recordable S₃. Although recordable in 38.6% of the 44 subjects over 40 years old, the physiologic S₃ found in adults was less intense and occurred later in diastole when compared with that in children and adolescents. Marked changes in left ventricular filling hemodynamics were observed with aging, including an increase in left ventricular wall thickness and mass, a prolongation of the left ventricular isovolumetric relaxation period, a decrease in left ventricular early diastolic filling and wall thinning rates, and a reduction in the height and steepness of the rapid filling wave measured on the calibrated left apexcardiogram (linear correlation with age significant at p < .001 for all parameters). Although less pronounced, these changes were very similar to the diastolic abnormalities found in patients with pressure overload left ventricular hypertrophy. Therefore, the higher pressure load imposed on the left ventricular wall due to the well-known gradual increase in blood pressure that occurs during normal growth and adulthood appears to be the most likely explanation for the observed changes in diastolic filling. It is concluded that the later occurrence, the diminishing amplitude, and the eventual complete disappearance of the physiologic S₃ with age results from a decrease in early diastolic left ventricular filling and subsequent deceleration of inflow caused by the development of relative left ventricular hypertrophy in adulthood as compared with childhood.


THE THIRD heart sound (S₃) consists of a group of low-frequency vibrations (20 to 70 Hz) occurring in early diastole at an average of 150 msec (range 100 to 240 msec) after closure of the aortic valve. It is well known that the S₃ is frequently audible in normal children and adolescents. However, its presence in individuals over the age of 40 years is usually associated with underlying heart disease such as left ventricular failure of various origins or excessive flow through the mitral valve in early diastole (e.g., mitral regurgitation, ventricular septal defect, and patent ductus arteriosus). Conditions associated with high cardiac output (e.g., hyperthyroidism, anemia, fever, and pregnancy) may also give rise to an S₃. Except for the earlier occurrence of a high-pitched S₃ in patients with constrictive pericarditis (pericardial knock), no manifest differences in timing and quality of physiologic and pathologic S₃,8 have been reported. Therefore, theories on the genesis of the pathologic S₃ should also offer a reasonable explanation for the occurrence and disappearance of its physiologic counterpart.

Recently we have demonstrated that the vibrations of the S₃ occur during rapid deceleration of left ventricular inflow due to a reversed (backward) transmitral pressure gradient caused by a limitation of filling imposed by the left ventricular wall.1 The amplitude of this adverse pressure gradient, and hence the amount of deceleration, depends on the height and steepness of the increase in left ventricular pressure after minimum diastolic pressure, or the so-called rapid filling wave (RFW). This RFW is determined by the preceding amount of inflow, by the completeness of relaxation, and by the viscoelastic properties of the left ventricular myocardium.2–4 Based on this reasoning we tried to find age-related changes in left ventricular diastolic function and filling hemodynamics that might offer an
explanation for the presence and disappearance of the physiologic $S_3$.

Methods

Subjects. The study material consisted of school children, nurses, medical students, medical doctors, and healthy employees from an insurance company. One hundred thirty-eight male and 27 female subjects participated, for a total of 165. To study the effects of age on the prevalence and the determinants of the physiologic $S_3$, healthy young individuals of approximately 6, 12, 18, 24, 30, and 36 years of age were selected for the study (groups I to VI). A control group consisted of healthy middle-aged subjects between 40 and 62 years old (group VII). Mean ages and clinical data on the different groups are given in table 1.

All subjects were free of history or physical findings suggestive of cardiovascular disease, including hypertension, and in each 12-lead electrocardiographic findings were within normal limits for the age of the individual. The presence of clinical abnormalities, a blood pressure equal to or higher than 140/80 mm Hg, or a dubious electrocardiogram resulted in exclusion from the study.

Methodology and measurements. On an eight-channel ink-jet recorder (Siemens-Elema 82), phonocardiograms from the cardiac base and apex were recorded in different frequency ranges with Mannheimer filters with nominal frequencies of 25, 50, 100, 200, and 400 Hz. An $S_3$ was considered to be present whenever characteristic low-frequency vibrations of more than 10% of the height of the second heart sound ($S_2$) were recorded in the 25 Hz band (figure 1). A similar definition has been used for the fourth heart sound ($S_4$) and was found to be adequate for the elimination of baseline noise in the 25 Hz band. The ratio of the maximum deflection of $S_2$ and $S_1$ at the apex in the 25 Hz frequency band ($S_2/S_1$) was measured and used as a relative index for the intensity of the physiologic $S_3$.

The left apexcardiogram and the jugular venous pulse were recorded with a displacement transducer (Siemens 860). An electronic (a ramp signal with a constant slope) and a mechanical (the displacement of a fixed air volume of 20 mm$^3$) calibration signal transmitted through the same differentiating circuit as the recorded pulse allowed calibration of the height and the first time derivative of the left apexcardiogram (expressed in mm$^3$ and mm$^3$/sec, respectively).

The following measurements were obtained: total height and peak first derivative of the RFW of the left apexcardiogram (expressed in mm$^3$ and mm$^3$/sec, respectively); the heights of the RFW and A waves expressed as a percentage of the total height of the left apexcardiogram; and the time intervals (msec) from the onset of $S_2$ to the protodiastolic nadir of the left apexcardiogram ($S_2-O$), to the peak of the $v$ wave of the jugular pulse ($S_2-v$), and to the onset of $S_1$ ($S_2-S_3$) and from the protodiastolic nadir to the peak of the RFW of the left apexcardiogram (O-F or duration of RFW).

M mode echocardiograms were recorded during mild expiration from the left sternal border with a 2.25 MHz transducer and an Irex system II ultrasonic unit. A phonocardiogram from the apical region was recorded simultaneously on the photographic paper. Depending on the requirements, paper speed was 50, 75, or 100 mm/sec. Recordings were made with the transducer in the four classic positions on the chest.

The echocardiograms were processed with the use of a digitizer and a computer program as previously reported. The analyses were done on three successive beats and the values were

![FIGURE 1](http://circ.ahajournals.org/)

FIGURE 1. Typical phonocardiographic recording in an 18-year-old boy with a physiologic $S_3$. 25, 50, 100, 200 Hz = frequency bands with Mannheimer filters with different nominal frequencies.
then averaged. The following measurements (leading-edge method) were obtained at end-diastole and end-systole: internal dimension, septal thickness, and posterior wall thickness.

The maximum rate of increase in left ventricular dimension in early diastole was computed and then normalized by dividing the maximum rate by the instantaneous diastolic dimension as max dD/dt/D (sec^-1). Similarly, the maximum normalized thinning rate of the posterior wall was calculated as max dPW/dt/PW (sec^-1). This normalization technique allows for correction of the indexes for physiologic variations in left ventricular size and wall thickness. In addition, fractional shortening (FS%), left ventricular mass (g), and the time interval (msec) from the onset of S₂ to the beginning of mitral valve opening (isovolumetric relaxation period or IVRP) were calculated.

**Statistical analysis.** Data are expressed as mean ± SD. For each parameter an F value (one-way analysis of variance) and a linear correlation coefficient for the relationship with age were computed and evaluated for statistical significance in the total population (group I to VII) and in the groups of fully grown subjects (groups IV to VII) separately. In addition, linear discriminant analysis was applied to identify the combination of anthropometric and hemodynamic variables providing an accurate prediction of the presence or absence of a physiologic S₃.

**Results**

Age, resting heart rate, and anthropometric data (weight, height, circumference of thorax during full expiration, and body surface area) are given in table 1. In the total population each of these parameters was significantly correlated with age. In fully grown subjects (groups IV to VII) no significant differences were found with respect to weight, height, body surface area, or heart rate. Circumference of the thorax during expiration, however, increased significantly from group IV to VII. A physiologic S₃ was present in all individuals of groups I to III. In the great majority of individuals belonging to groups IV to VI an S₃ could also be recorded. In group VII, an S₃ was observed in 17 of 44 subjects (38.6%) (table 2). In all cases the vibrations of the S₃ occurred during the initial part of the E-F closing slope of the mitral valve on the echocardiogram (figure 2). The time interval S₂-S₃ and amplitude ratio S₂/S₃ increased with aging, indicating a less intense and more delayed physiologic S₃ in older individuals (table 2).

Highly significant age-related changes in isovolumetric relaxation were observed. The left ventricular IVRP measured on the M mode echocardiogram, the S₂-O, and the S₂-V (an indirect measure of the right ventricular relaxation period) increased significantly with age not only in the total population studied, but also in the groups of adults (IV to VII) with a nearly identical heart rate (table 2). The height and the peak derivative of the RFW significantly decreased with age (also in groups IV to VII), while the duration of O-F significantly increased (table 2).

As expected, internal diameter, septal and posterior wall thickness, and left ventricular mass all increased

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Anthropometric data and resting heart rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>(n = 20)</td>
</tr>
<tr>
<td>Group II</td>
</tr>
<tr>
<td>(n = 18)</td>
</tr>
<tr>
<td>Group III</td>
</tr>
<tr>
<td>(n = 21)</td>
</tr>
<tr>
<td>Group IV</td>
</tr>
<tr>
<td>(n = 19)</td>
</tr>
<tr>
<td>Group V</td>
</tr>
<tr>
<td>(n = 21)</td>
</tr>
<tr>
<td>Group VI</td>
</tr>
<tr>
<td>(n = 22)</td>
</tr>
<tr>
<td>Group VII</td>
</tr>
<tr>
<td>(n = 44)</td>
</tr>
</tbody>
</table>

F = body surface area; HR = heart rate; r and r' = linear correlation coefficients with age for all groups and for groups IV to VII, respectively; F and F' = F ratio for all groups and for groups IV to VII, respectively.

*p < .001.
with age in the total population. When adults were considered separately the left ventricular wall thickness and mass further increased with advancing age while the end-systolic internal diameter decreased (table 3).

In accordance with the observed changes in relaxation times, the normalized thinning rate of the posterior wall also significantly decreased with age in the groups of fully grown individuals. In the total population the normalized maximum rate of increase in left ventricular dimension decreased significantly with age. Between groups IV to VII the differences were statistically insignificant (table 3).

FS% increased with aging and this increase was most pronounced in the groups of adults (table 3).

When the height of the RFW and the A wave (both expressed as percent of the total height of the left apexcardiogram) were considered together, opposite changes with aging were found in groups IV to VII (figure 3).

Discriminant analysis was applied to data from groups IV to VII to attempt to predict the presence or absence of an S₃ from the anthropometric and hemodynamic parameters measured in this study. Groups I to III were not taken into account for this analysis since all subjects in these groups presented an S₃. Parameters selected for inclusion in the model were age, weight, height, circumference of the thorax during full expiration, body surface area, heart rate, left ventricular septal and posterior wall thickness, internal dimensions at end-systole and end-diastole, left ventricular mass, FS%, the maximum normalized rate of increase in left ventricular dimension in early diastole, the maximum normalized thinning rate of the posterior wall, the time intervals S₂₋₋, S₂₋, O₋₋, and the IVRP, the total height and the peak first derivative of the RFW, and the height of RFW and the A wave expressed as a percent of the total deflection of the apexcardiogram.

Age, the IVRP of the left ventricle, and O₋₋ were the only parameters that provided significant discrimination between subjects with and without an S₃ (table 4).

**Discussion**

The prevalence of the physiologic S₃. In the present study an S₃ was recordable in nearly all subjects below the age of 36 years and in 38.6% of the normal adults with a mean age of 47.7 years (range 40 to 62 years). However, the amplitude of the S₃ was significantly smaller in adults than in children or adolescents and its time delay after the S₂ significantly increased with aging, even in the groups with identical heart rates.

Although we did not establish the relationship between recordability and audibility, it is very likely that many of the S₃s recorded in normal subjects over age 40 would have been inaudible. Thus, our observations do not invalidate the clinical axiom that an S₃ heard in an individual over the age of 40 years usually indicates underlying heart disease. In the other hand, whether audible or not, the characteristic low-frequency vibrations recorded in 38.6% of normal subjects over the age of 40 were very similar to the vibrations recorded in younger subjects with an audible S₃, and therefore can be considered as the external phonocardiographic manifestations of the same process in early diastole.

**Age-related changes in left ventricular filling hemodynamics.** Phonomechanocardiographic and echocardiographic...
FIGURE 2. Time relationship between mitral valve movement and S₃. Simultaneous recording of the M mode echocardiogram and the external phonocardiogram (low-frequency band) in the same subject as in figure 1. The vibrations of the S₃ occur during the initial part of the E-F closing slope of the mitral valve (MV). RV = right ventricular cavity; LV = left ventricular cavity; ST = septum; PW = posterior wall; E = maximum opening of the anterior leaflet of the mitral valve.

TABLE 3

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>max dD/dt/D (sec⁻¹)</th>
<th>max dPW/dt/PW (sec⁻¹)</th>
<th>FS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dd and Ds = left ventricular internal diameter at end-diastole and end-systole; STd and STs = left ventricular septum thickness at end-diastole and end-systole; PWd and PWs = left ventricular posterior wall thickness at end-diastole and end-systole; LV = left ventricular mass; max dD/dt/D = peak normalized increase of dimension in early diastole; max dPW/dt/PW = peak normalized thinning rate of the posterior wall in early diastole; r, r', F, and F' are as in table 1.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.7 ± 2.8</td>
<td>25.1 ± 2.3</td>
<td>6.0 ± 0.7</td>
<td>8.4 ± 0.7</td>
</tr>
<tr>
<td>Group II</td>
<td>43.3 ± 3.6</td>
<td>28.5 ± 2.7</td>
<td>7.2 ± 0.8</td>
</tr>
<tr>
<td>Group III</td>
<td>48.4 ± 3.8</td>
<td>31.9 ± 2.7</td>
<td>8.3 ± 0.9</td>
</tr>
<tr>
<td>Group IV</td>
<td>50.3 ± 2.9</td>
<td>34.1 ± 3.4</td>
<td>7.6 ± 1.0</td>
</tr>
<tr>
<td>Group V</td>
<td>49.8 ± 2.9</td>
<td>32.4 ± 2.3</td>
<td>8.3 ± 1.4</td>
</tr>
<tr>
<td>Group VI</td>
<td>51.6 ± 4.5</td>
<td>33.4 ± 3.2</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td>Group VII</td>
<td>49.2 ± 4.5</td>
<td>30.6 ± 3.6</td>
<td>9.3 ± 1.5</td>
</tr>
<tr>
<td>F</td>
<td>34.8b</td>
<td>21.4b</td>
<td>23.0b</td>
</tr>
<tr>
<td>r</td>
<td>.54b</td>
<td>.30b</td>
<td>.66b</td>
</tr>
<tr>
<td>F'</td>
<td>1.8 (NS)</td>
<td>6.6b</td>
<td>9.6b</td>
</tr>
<tr>
<td>r'</td>
<td>-.10(NS)</td>
<td>-.36b</td>
<td>.52b</td>
</tr>
</tbody>
</table>

Dd and Ds = left ventricular internal diameter at end-diastole and end-systole; STd and STs = left ventricular septum thickness at end-diastole and end-systole; PWd and PWs = left ventricular posterior wall thickness at end-diastole and end-systole; LV = left ventricular mass; max dD/dt/D = peak normalized increase of dimension in early diastole; max dPW/dt/PW = peak normalized thinning rate of the posterior wall in early diastole; r, r', F, and F' are as in table 1.

aP < .01; bP < .001.
graphic examinations revealed marked age-related changes in filling hemodynamics. In the total population of this study, isovolumetric relaxation times of the right and left ventricles (measured by different techniques) significantly increased with age. In concert with these findings the normalized maximum thinning rate of the left ventricular wall and the normalized maximum rate of increase in left ventricular dimension in early diastole decreased with advancing age. In a group of normal subjects from 4 to 75 years old, Fifer et al. also reported a significant negative correlation between age and left ventricular filling and wall thinning rates derived from M mode echocardiograms. These age-related changes in the left ventricular diastolic properties are remarkably similar, although less pronounced, than the abnormalities observed in patients with left ventricular hypertrophy due to pressure overload. Indeed, pressure overload hypertrophy was found to be associated with a reduced early diastolic relaxation and filling rate and a compensatory increased atrial contribution to filling.13-20

In the present study left ventricular wall thickness and mass significantly increased with age, not only within the total population but also within the groups of adults. These results strongly suggest the development of relative left ventricular hypertrophy during normal adulthood as compared with childhood or adolescence.

None of the individuals in the present study had a history of hypertension or electrocardiographic evidence of left ventricular hypertrophy. Blood pressures measured at the time of the noninvasive examinations were all below 140/80 mm Hg. Large population studies performed in children and adolescents with standardized methods have shown that systolic, and to a lesser extent diastolic blood pressures, significantly increase with age in both sexes.21,22 Thus, an increased pressure load on the left ventricle with advancing age appears to be the most likely explanation for the development of relative hypertrophy during adulthood and for the observed changes in diastolic filling dynamics.

As already discussed, the reduced early diastolic filling due to impaired relaxation in patients with pressure overload left ventricular hypertrophy is compensated for by an increased atrial contribution to filling. Both the reduced distensibility of the left ventricular wall and the increased filling rate during atrial contraction explain the presence of an increased A wave on the left ventricular pressure tracing and the left apexcardiogram and the frequent appearance of an atrial gallop in these patients.5 Recently Miyatake et al., using two-dimensional Doppler echocardiography, have studied the influence of aging on left ventricular filling and have found changes remarkably similar to those observed in patients with left ventricular hypertrophy in older individuals. These authors found that the ratio of peak left ventricular inflow velocity in the atrial contraction phase to the peak inflow velocity in early diastole significantly increased with age in a group of 69 normal subjects between 22 and 69 years old (mean 46 years). The gradual decrease in the RFW and the parallel increase of the A wave with increased age in our study (figure 3) are in keeping with the Doppler echocardiographic results and indirectly reflect the left ventricular pressure changes in response to the changed filling pattern in diastole.

The mechanism of disappearance of the physiologic S3. Although a number of extracardiac and technical factors are certainly involved, the diastolic waves of the left apexcardiogram are mainly determined by the corresponding changes in left ventricular pressure24-26 that occur as the result of a complex interaction between filling rate, completeness of relaxation, and viscoelastic properties of the left ventricular wall.2 As we have shown recently, the pressure increases in the RFW and the A wave are responsible for a reversal of

---

**TABLE 4**

<table>
<thead>
<tr>
<th>Variables</th>
<th>With $S_3$ (n = 67)</th>
<th>Without $S_3$ (n = 24)</th>
<th>$b_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1VRP (msec)</td>
<td>71.9</td>
<td>84.7</td>
<td>-0.118</td>
</tr>
<tr>
<td>O-F (msec)</td>
<td>60.9</td>
<td>72.9</td>
<td>-0.127</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.4</td>
<td>45.0</td>
<td>-0.096</td>
</tr>
</tbody>
</table>

$\text{b}_1$ = discriminant function coefficient; $F = 23.91$ (p < .001); $D^2$ (Mahalanobis distance) = 4.153.
the transmitral pressure gradient and hence for the rapid deceleration of left ventricular inflow in early and late diastole.1

Thus, the present results together with the recent findings of Fifer et al.12 and Miyatake et al.23 point to a reduced left ventricular filling rate and a less rapid deceleration of inflow in early diastole and to a compensatory increased inflow and deceleration rate at the time of atrial contraction with advancing age. Since the vibration of S3 and S4 occur during and, in our opinion, are caused by these rapid decelerations, the gradual decrease in intensity, the later occurrence in diastole, and the eventual complete disappearance of the physiologic S3 during adulthood together with the reappearance of an S4 in older individuals27 can be reasonably explained. A more rapid left ventricular relaxation rate due to a higher sympathetic tone could be a valid explanation for the rapid filling and subsequent more sudden halting or deceleration of inflow in early diastole and thus for the presence of a physiologic S3 in younger subjects.

Linear discriminant analysis was applied to identify anthropometric and/or hemodynamic parameters that could be used for predicting the presence or absence of a physiologic S3. The combination of age, left ventricular IVRP (a major determinant of early diastolic filling rate), and the duration of the RFW on the left apexcardiogram (a noninvasive measure of sudden halting or deceleration of early ventricular inflow) provided maximum discrimination between subjects with and without a physiologic S3. These results strongly support the proposed mechanism of disappearance of the physiologic S3. In this respect it is important to note that, in spite of significant differences between the groups, the circumstance of the thorax during full expiration was of no value in discriminating between subjects with and without an S3.

The lack of discriminatory value of the circumstance of the thorax, the almost linear increase with age in the time delay between S3 and S4 (irrespective of heart rate), and the observation that an S4 can be recorded directly from the freely exposed left ventricular wall,1,38 without any contact with the thoracic wall, strongly argue against the hypothesis that the S4 simply results from early diastolic impact on the chest wall and that diminishing impact with advancing age explains the disappearance of a physiologic S3.29

Recently it was demonstrated that the presence of the S4 was associated with an abrupt termination of an enhanced left ventricular long-axis filling activity in early diastole.28, 30, 31 It is possible that the age-related changes in diastolic properties of the left ventricular wall observed in the present study run parallel with a gradual decrease in longitudinal expansion capacity during early filling. Since we have only measured short-axis changes we could not test this hypothesis in our population. Both concepts can be considered complementary and concern the same basic mechanism: limitation of filling imposed by the left ventricular wall.

In conclusion, the disappearance of a physiologic S3 with advancing age was associated with distinct age-related changes in left ventricular filling hemodynamics. The characteristics of these changes can be summarized as being the result of the development of relative left ventricular hypertrophy during adulthood as compared with childhood. Although there is no proven relationship, a higher pressure load imposed on the left ventricle due to the gradual increase in blood pressure during normal growth and adulthood seems the most likely explanation for the observed changes. The proposed mechanism of disappearance is consistent with our previously reported hypothesis on the genesis of gallop sounds.1,2 Moreover, it also provides a reasonable explanation for the occurrence of an S3 in older individuals.27 Furthermore, this mechanism fits perfectly into the unitarian concept of the genesis of heart sounds, according to which heart sounds are considered vibrations of the cardiohemic system due to acceleration or deceleration of blood in response to pressure changes.32

We are indebted to Mrs. Roos Struyven and Mrs. Agnes Goethuys for assistance in the preparation of the manuscript and to Dr. F. Pollefeyt of the Belgische Boerenbond for assistance in conducting the study.

References
8. Teichholz LE, Kreulen T, Herman MV, Gorlin R: Problems in

Vol. 73, No. 5, May 1986
VAN DE WERF et al.

echocardiographic volume determinations: echocardiographic-an
giographic correlations in the presence or absence of asynergy. Am J Cardiol 37: 7, 1976
The mechanism of disappearance of the physiologic third heart sound with age.
F Van de Werf, J Geboers, H Kesteloot, H De Geest and L Barrios

Circulation. 1986;73:877-884
doi: 10.1161/01.CIR.73.5.877

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/73/5/877

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/