Aortic Root Dilatation and Mitral Valve Prolapse in Marfan's Syndrome

An Echocardiographic Study


SUMMARY

Echocardiographic and phonocardiographic findings in 35 patients with Marfan's Syndrome and ten patients without Marfan's or other clinically apparent connective tissue disorders but with angiographic and echocardiographic evidence of mitral prolapse are reported and compared. Echocardiography revealed aortic root dilatation and/or mitral valve prolapse in 97% of the patients with Marfan's Syndrome. Aortic root dilatation was found in 60% of this group (74% of males, 33% of females) while mitral valve prolapse was found in 91% (87% of males, 100% of females). The incidence of aortic dilatation and mitral prolapse in patients with Marfan's Syndrome was essentially equal in children and adults of the same sex. None of the nine adults or one child with mitral prolapse but without evidence of Marfan's Syndrome or other clinically apparent connective tissue disorder had aortic root enlargement.

Auscultatory examination and phonocardiography revealed abnormalities in 54% of the patients with Marfan's Syndrome. Aortic regurgitation was found in 23% of this group (35% of males, 0% of females) while mitral regurgitation and/or mitral clicks were found in 46% (39% of males, 58% of females). Aortic regurgitation was much more frequent in adult males with Marfan's Syndrome (7/14, 50%) than male children (1/9, 11%), while the incidence of abnormal mitral sounds was essentially the same in adults (33% of males, 60% of females) and children (43% of males, 57% of females) of the same sex with Marfan's Syndrome. Abnormal mitral sounds were more frequent in patients without Marfan's who had mitral prolapse (90%) than in those with Marfan's (46%).

It appears that cardiac abnormalities are a consistent manifestation of Marfan's Syndrome and that ultrasound is a more sensitive indicator of these abnormalities in such patients than auscultation or phonocardiography.

PREVIOUS REPORTS based upon auscultatory and angiographic findings have noted mitral regurgitation and aortic root dilatation in patients with Marfan's Syndrome.1,2,3 Due to the invasive nature of angiography, sampling of the Marfan's patient population by these techniques has been somewhat limited. Three major retrospective surveys relying on necropsy or noninvasive parameters other than ultrasound have reported aortic root dilatation, aortic regurgitation and/or mitral regurgitation in 61%,4 40%5 and 32%6 of the Marfan's patient population studied.

This report describes echocardiographic and phonocardiographic findings in 35 patients with skeletal and/or ocular confirmation of Marfan's Syndrome and a family history of the disorder. In addition ten patients without Marfan's but with angiographic evidence of mitral prolapse were studied and the findings compared to those patients with Marfan's Syndrome. This study represents the first reported survey of this syndrome utilizing cardiac ultrasound for noninvasive quantitation of aortic size and evaluation of mitral valve function.

Methods and Techniques

Patient Selection

Thirty-five patients with Marfan's Syndrome underwent echocardiographic, phonocardiographic, and auscultatory examination. The diagnosis of Marfan's Syndrome was based on the presence of both skeletal (arachnodactyly and dolichostenomelia) and ocular (lens dislocation) abnormalities (27 patients), or on skeletal abnormalities alone if a well-documented family history of Marfan's Syndrome existed (eight patients). The 35 patients selected for analysis represent all available patients on record at this institution who met these criteria at the time of this study.

This patient group consisted of 23 males and 12 females. Nine of the males and five of the females were less than 16
years of age. The mean age of the males was 20.9 years ± 11.8 years with a range of 5 to 52 years. The mean age of the females was 20.9 years ± 15.4 years with a range of 5 to 61 years.

Ten additional patients without evidence of Marfan’s Syndrome underwent echocardiographic, phonocardiographic, and auscultatory examination. These patients were selected on the basis of angiographic evidence of mitral valve prolapse, the complete absence of any clinical or familial evidence of Marfan’s Syndrome or any other connective tissue disorder, and the quality of the echographic record.

This patient group consisted of four males and six females. One of the males and none of the females were less than 16 years of age. The mean age of the males was 31.8 years ± 20.9 years with a range of 7 to 51 years. The mean age of the females was 45.5 years ± 14.5 years with a range of 26 to 62 years.

Techniques

Echocardiograms were performed utilizing a Picker Echoview 10 Ultrasonoscope with a 2.25 MHz transducer of 0.5 inch diameter with an acoustic lens collimating the sound beam at 5 cm tissue depth. The echocardiograms were recorded on either an Electronics for Medicine DR12 or a Honeywell #1856 strip chart recorder. All patients were studied in the supine position with the transducer placed on the chest wall at the left sternal border. The ideal transducer location was the point at which the anterior and posterior mitral valve leaflets could be recorded with the transducer held nearly perpendicular to the chest wall. Slight rocking of the transducer in a superior and medial fashion allowed recording of the aortic root. Great care was taken to note transducer orientation when recording movement of the mitral valve. Findings noted in this study are those obtained when the anterior and posterior mitral valve leaflets were recorded with the transducer held perpendicular to the chest wall.

Phonocardiograms were recorded on an Electronics for Medicine DR12 or a Sanborn 550M recorder with Maico contact microphones placed at the cardiac apex, left lower sternal border, and second left sternal position with a bandpass filter to display a frequency range of 40 to 500 Hz.

Auscultatory examinations were conducted by two different observers who were unaware of the phonocardiographic or echocardiographic findings.

Measurements and Standards

Aortic root and left atrial dimensions were measured as previously described. The aorta was measured from the most anterior portion of the anterior aortic wall to the most anterior portion of the posterior aortic wall at end diastole. The left atrium was measured from the most anterior portion of the posterior aortic wall to the most anterior portion of the left atrial wall at end systole.

Previously established criteria used for evaluation of aortic root size are given in table 1. Aortic root dimensions which were abnormally large by at least two of the three criteria as in figure 1 were considered positive for aortic root enlargement. All other positive and negative combinations of the criteria were considered as negative for aortic root enlargement.

Systolic mitral valve motion was assessed by existing criteria. Normal valve motion was defined as being anterior from the onset of mechanical systole as indicated by movement of the left ventricular posterior wall. Valve motion which was posterior from the onset of mechanical systole

and which reached its most posterior point at mid-systole was designated a “whole systolic” or “hammock” prolapse of the mitral valve (fig. 2). Valve motion which moved abruptly posterior during the last two-thirds of mechanical systole was designated a “mid-systolic” prolapse of the mitral valve (fig. 3).

Figure 1

Echocardiogram of the aortic root in a patient with Marfan’s Syndrome. Ant AoW = anterior aortic wall; Post AoW = posterior aortic wall; AoV = aortic valve; ecg = electrocardiogram; LAw = left atrial wall.
Results

Echocardiographic

The echocardiographic findings in patients with Marfan's Syndrome are summarized in table 2 and figure 4. Thirty-four of thirty-five patients with Marfan's Syndrome had a dilated aortic root, mitral valve prolapse, or both. The remaining patient in the group studied had an aortic root dimension at the outer limits of normal and no mitral valve prolapse. Aortic root dilatation was found in 21 of 35 (60%) of the patients and was more common in males (17 of 23) than in females (4 of 12). There was no significant difference between the incidence of aortic root enlargement in children and adults of the same sex.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child</td>
<td>Adult</td>
</tr>
<tr>
<td>With Marfan's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Aortic root enlargement only</td>
<td>0 (0%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Mitral valve prolapse only</td>
<td>2 (22%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Aortic root enlargement and mitral valve prolapse</td>
<td>7 (78%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Total patients with cardiac abnormalities</td>
<td>9 (100%)</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Without Marfan's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Aortic root enlargement only</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mitral valve prolapse only</td>
<td>1 (100%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Aortic root enlargement and mitral valve prolapse</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total patients with cardiac abnormalities</td>
<td>1 (100%)</td>
<td>3 (100%)</td>
</tr>
</tbody>
</table>

Circulation, Volume 52, October 1975
The aortic root dimensions of all adults (≥ 16 years) are illustrated. Dots = patients with Marfan's Syndrome; Squares = patients with prolapse but without Marfan's Syndrome or other connective tissue disorder. The dotted horizontal line denotes the outer limits of normal. Points anterior to this line represent aortic root enlargement by the three criteria used. The patients were classified as having aortic root enlargement only if the aortic root dimensions exceeded at least two of the normal values used. To be noted are patients just above or just below the normal values. Most patients with Marfan's Syndrome classified as having aortic root enlargement exceeded all three of the normal criteria used or exceeded two of the criteria by a large amount. Patients without Marfan's but with mitral prolapse who were near the outer limit of normal by one criterion, were usually well within normal limits by the remaining two criteria. BSA = body surface area, cm = centimeters, M² = meters squared, LA = left atrium, Ao = aortic root.

Aortic root dilatation (2 mitral prolapse (3 was males). Three of the 23 male patients and four of 12 female patients without a murmur of aortic regurgitation had aortic root dilatation. Aortic wall thickness was ≤ 3 mm in all patients. There was no echocographic evidence of aortic root dissection or bicuspid aortic valve in this patient group.7 9

Mural regurgitation was found in five of 12 females, while combined aortic root dilatation and mitral valve prolapse was found in four of 12 females.

All ten patients without Marfan's Syndrome but with angiographic evidence of mitral valve prolapse appeared to have an echocardiographic pattern of mitral prolapse. Seven of this group had a whole systolic prolapse. The remaining three had a midsystolic prolapse. No patient in this group had echocardiographic or angiographic evidence of aortic root dilatation. Aortic wall thickness was ≤ 3 mm in all patients. There was no echocographic evidence of aortic root dissection or bicuspid aortic valve in this patient group.7 9

Auscultatory examination and phonocardiography revealed abnormalities in 54% of the patients with Marfan's Syndrome (table 3). A murmur of aortic regurgitation was only noted in males (8 of 23). Of the eight males with a murmur of aortic regurgitation, seven were more than 16 years of age (50% of all adult males) while only one was less than or equal to 16 years of age (11% of all male children). Six of eight male patients with a murmur of aortic regurgitation had aortic root dilatation by ultrasound; however, 11 of 15 male patients and four of 12 female patients without a murmur of aortic regurgitation had aortic root enlargement. No consistent correlation between degree of aortic root enlargement and presence of an aortic regurgitation murmur could be found.

A murmur of mitral regurgitation and/or systolic clicks were found in 46% of the patients with Marfan's Syndrome (9 of 23 males and 7 of 12 females). There was no significant difference in the incidence of mitral murmurs and/or clicks in adults and children of the same sex.

The predominant auscultatory abnormalities in patients with Marfan's Syndrome varied with sex. Five of 23 males had combined aortic and mitral abnormalities while four of 23 had isolated mitral abnormalities and three of 23 had isolated aortic abnormalities. Females in this series had only mitral abnormalities by auscultation and phonocardiography (7 of 12).

A murmur of mitral regurgitation and/or systolic clicks were found in nine of the ten patients without Marfan's Syndrome in whom angiographic and echocardiographic evidence of systolic mitral valve prolapse were found. Mitral clicks and murmurs occurred with equal frequency in males and females.

Discussion

Echocardiographic findings in this study indicate that cardiac abnormalities are far more common than...
FEATURES OF Aortic root described demonstrated in males. Marfan's Syndrome was not particular cardiac abnormalities were found in the female sex. As seen in table 2, while aortic dilata

The incidence of aortic root enlargement is of particular interest. As seen in table 2, while aortic dilatation was not found in any of the nine adults or one child without clinical evidence of Marfan's Syndrome or other connective tissue disorder, aortic root dilatation was found in nearly three-fourths of the male population and one-third of the female population with Marfan's Syndrome. It would appear that aortic root dilation is a sex-linked variable in patients with Marfan's Syndrome which is more predominant in males.

It also appears that early aortic dilatation in patients with Marfan's Syndrome may progress with age in males, as suggested by McKusick, eventually leading to aortic regurgitation in some. This inference is supported by an equal incidence of aortic root dilatation in male children and adults (7 of 9 male children, 10 of 14 adult males) while aortic regurgitation was far more prevalent in the adult male (1 of 9 male children, 7 of 14 adult males) as seen in table 3. Absence of aortic regurgitation in females may imply a lack of appreciable progression of aortic root dilatation in the female sex.

No consistent relationship between a murmur of aortic regurgitation and the degree of echocardiographic aortic root dilatation could be found. Most patients with aortic regurgitation had aortic root dilatation; however, many patients without a murmur of aortic regurgitation also had aortic root dilatation. This finding points out the pitfall in screening patients for aortic abnormalities by auscultation.

Some comment should be made as to the accuracy of the echocardiographic criteria employed to assess aortic root size. Normal values of echocardiographic aortic root size in adults have been established, yet there is a wide "normal" range which might mask mild

Table 3

Auscultatory Findings in Patients with and without Marfan's Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child</td>
<td>Adult</td>
<td>All</td>
<td>Child</td>
<td>Adult</td>
</tr>
<tr>
<td>With Marfan's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>9 (100%)</td>
<td>14 (100%)</td>
<td>23 (100%)</td>
<td>5 (100%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>1. Aortic regurgitation only</td>
<td>0 (0%)</td>
<td>3 (21%)</td>
<td>3 (31%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>2. Mitral abnormalities only (click, click, murmur, murmur)</td>
<td>2 (22%)</td>
<td>2 (14%)</td>
<td>4 (17%)</td>
<td>3 (60%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>3. Aortic and mitral abnormalities</td>
<td>1 (11%)</td>
<td>4 (29%)</td>
<td>5 (22%)</td>
<td>0 (0%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Total patients with cardiac abnormalities</td>
<td>3 (33%)</td>
<td>9 (64%)</td>
<td>12 (52%)</td>
<td>3 (60%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Without Marfan's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>1 (100%)</td>
<td>3 (100%)</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1. Aortic regurgitation only</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2. Mitral abnormalities only (click, click, murmur, murmur)</td>
<td>1 (100%)</td>
<td>3 (100%)</td>
<td>4 (100%)</td>
<td>5 (80%)</td>
<td>5 (80%)</td>
</tr>
<tr>
<td>3. Aortic and mitral abnormalities</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total patients with cardiac abnormalities</td>
<td>1 (100%)</td>
<td>3 (100%)</td>
<td>4 (100%)</td>
<td>5 (80%)</td>
<td>5 (80%)</td>
</tr>
</tbody>
</table>

Cardiac Abnormalities in Marfan's Syndrome

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Method of survey</th>
<th>Year of study</th>
<th>No. of patients</th>
<th>Age range</th>
<th>Cardiac abnormalities</th>
<th>Ocular abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rados, A.</td>
<td>Lit. review</td>
<td>1942</td>
<td>204 (100 M, 104 F)</td>
<td>5 wks–61 yrs</td>
<td>32%</td>
<td>62%</td>
</tr>
<tr>
<td>Goyette, E.</td>
<td>Autopsy</td>
<td>1933</td>
<td>34 (?M, 7?F)</td>
<td>?</td>
<td>30–60%</td>
<td>50–75%</td>
</tr>
<tr>
<td>McKusick, V.</td>
<td>Auscultation and autopsy</td>
<td>1955</td>
<td>105 (?M, ?F)</td>
<td>?</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Phonyphutkul, C.</td>
<td>Auscultation</td>
<td>1973</td>
<td>36 (16 M, 20 F)</td>
<td>1 day–15 yrs</td>
<td>61%</td>
<td>?</td>
</tr>
<tr>
<td>Brown, O.</td>
<td>Auscultation</td>
<td>1974</td>
<td>35 (23 M, 12 F)</td>
<td>3–61 yrs</td>
<td>54%</td>
<td>79%</td>
</tr>
<tr>
<td>Echoangiography</td>
<td>1974</td>
<td>35 (23 M, 12 F)</td>
<td>3–61 yrs</td>
<td>97%</td>
<td>79%</td>
<td></td>
</tr>
</tbody>
</table>
enlargement. Further, experience in our laboratory indicates that normal values in children are less reliable than those in adults because of the varying rates of development in children of different age groups. As a result, we utilized three previously established echocardiographic criteria for evaluating aortic root size in both adults and children (table 1). Most patients classified as having aortic root enlargement met all three of these criteria. There were, however, several patients who were at the outer limits of one or more of the normal criteria as seen in figure 4. Combined use of three sets of normal criteria usually categorized such patients as having no aortic root enlargement. Incidence of aortic root enlargement may, therefore, be slightly underestimated in this study because of a rigorous attempt to eliminate false positives. If for example the normal values were reduced by only 5%, the incidence of aortic root dilatation would be 90% rather than 74% in males, and 60%, rather than 33%, in females. Although considerable, these differences do not alter the observation of a higher incidence of aortic root enlargement in males than females. However, they do demonstrate the potential for a generally higher incidence of aortic root enlargement than estimated in this series. The wide normal range might also partially explain our inability to formulate a degree of aortic root dilatation which correlated with the degree of aortic regurgitation.

Mitral valve prolapse was found in all of the females and nearly all the males with Marfan’s Syndrome. This anomaly was the most frequently found cardiac abnormality in this patient group. Nearly all patients with this anomaly had a “whole systolic” variety of mitral prolapse. The preponderance of whole systolic prolapse and rare incidence of midsystolic prolapse in this connective tissue disorder may imply that this variety of prolapse results primarily from elongated mitral leaflets, elongated chordae tendineae or both. The incidence of mitral prolapse was the same in adults and children of the same sex, as was the incidence of abnormal mitral sounds. It appears that mitral prolapse in Marfan’s does not worsen to a point of mitral incompetence with age in most patients.

All patients with Marfan’s Syndrome in this study who had mitral clicks and/or murmurs had a mitral prolapse; however, about one-half of those patients with mitral prolapse had no abnormal auscultatory findings. As in the case of aortic dilatation, it appears that auscultation is a relatively insensitive way of assessing mitral valve function in patients with Marfan’s Syndrome. In contrast, abnormal mitral sounds were noted in most patients with mitral prolapse who had no evidence of Marfan’s Syndrome. This finding may imply a greater degree of prolapse, a more general prolapse, or perhaps a different mechanism of prolapse, in one of these two patient groups.

Echocardiographic detection of mitral valve prolapse was particularly easy in these patients. There were no equivocal or borderline records in this regard. It should be emphasized that transducer placement for examination of the mitral valve was carefully noted throughout this study. Only that data obtained with the transducer held perpendicular to the chest wall while observing motion of the anterior and posterior mitral leaflets was considered valid.

Auscultatory and phonocardiographic examinations revealed a far lower incidence of cardiac abnormalities than did echocardiographic examinations in patients with Marfan’s Syndrome (table 4). The variance between auscultatory and echocardiographic findings is not surprising. It has long been theorized that aortic root dilatation in patients with Marfan’s Syndrome precedes aortic regurgitation and that such dilatation is difficult to detect by routine chest X-ray in patients with arachnodactyly. In this regard ultrasound is probably more sensitive and quantitative in detection of aortic root enlargement than methods used in previous noninvasive surveys of patients with Marfan’s. Further, some cases of mitral valve prolapse without abnormal mitral sounds (clicks and/or murmurs) have also been previously reported. Our auscultatory findings reveal an incidence of auscultatory abnormalities which is similar to other studies of Marfan’s populations. Therefore, we presume ultrasound is more sensitive than auscultation in the detection of mitral valve abnormalities in this patient group.

Aortic root dilatation and mitral valve prolapse are significant clinical findings in patients with Marfan’s Syndrome. Several investigators have long noted that the aortic ring and adjacent intrapericardial portion of the aorta are first affected in diffuse aneurysm of the ascending aorta in Marfan’s15.16 Such dilatation has also been suggested as a prelude to aortic regurgitation in Marfan’s. Early echocardiographic detection of ring dilatation may then be of great clinical importance since these patients frequently develop profound aortic regurgitation with little or no dilatation of the ascending aorta shown by X-ray techniques. Left uncorrected, most patients developing aortic insufficiency under such circumstances succumb within two years after the onset of significant symptoms, making aortic regurgitation the most frequent cause of death in patients with Marfan’s.8 We suggest careful and frequent ultrasound examination of patients (particularly males) who have Marfan’s to evaluate changes in aortic root size which may occur in association with aortic regurgitation.

Mitrval valve prolapse may also represent a signifi-
ECHO FEATURES OF MARFAN’S SYNDROME

657

cant clinical finding in patients with Marfan’s Syndrome. We were unable to positively discern if the general classification of mitral prolapse worsens with age, although mitral regurgitation was not more prevalent in adults than children with Marfan’s Syndrome. Some cases of bacterial endocarditis have been associated with Marfan’s Syndrome. The high incidence of prolapse in these patients could be the predisposing factor to endocarditis.

In addition to their clinical importance, the high incidence of cardiac abnormalities in patients with Marfan’s Syndrome may provide a new diagnostic parameter for this connective tissue disorder. The diagnosis of Marfan’s Syndrome is often difficult if skeletal or ocular abnormalities are not apparent, even if a strong family history of the disorder is indicated. It appears that aortic root dilatation and/or mitral prolapse are at least as prevalent as ocular defects in Marfan’s Syndrome, making these deformities a major, rather than a minor component of this connective tissue disorder. This study illustrates that aortic root dilatation is not a consistently associated finding of mitral valve prolapse in adult patients without Marfan’s Syndrome or other clinically apparent connective tissue disorders. However, it is possible that aortic root dilatation and mitral prolapse may be present in other connective tissue disorders or in patients with certain congenital defects. Further, isolated mitral prolapse may be present in a small percentage of the normal patient population. However, in most cases we suggest that echocardiographic demonstration of aortic root dilatation or mitral prolapse with a well documented family history of Marfan’s Syndrome is diagnostic of the disorder or its forms frustes as would be skeletal or ocular abnormalities with a similar family history. If combined aortic root dilatation and mitral prolapse are found with appropriate family history, Marfan’s is even more strongly suggested. If the appropriate skeletal or ocular defects are also present, there is little doubt of the diagnosis of Marfan’s Syndrome. Echocardiographic recognition of cardiac abnormalities as a consistent finding in Marfan’s Syndrome may thus greatly enhance early diagnosis of this disorder or its forms frustes.

References


Circulation, Volume 52, October 1975
Aortic root dilatation and mitral valve prolapse in Marfan's syndrome: an ECHOCARDIOgraphic study.

Circulation. 1975;52:651-657
doi: 10.1161/01.CIR.52.4.651

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 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/52/4/651

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/