Evidence of Frank-Starling Effect in Man During Severe Semisupine Exercise

JAMES L. WEISS, M.D., MYRON L. WEISFELDT, M.D., STEVEN J. MASON, M.D.
JOHN B. GARRISON, PH.D., SUE V. LIVENGOOD, AND NICHOLAS J. FORTUIN, M.D.

SUMMARY Studies in man produce conflicting evidence of the role of the Frank-Starling mechanism in increasing cardiac output during exercise, though animal studies indicate that it may help to improve cardiac performance during severe exertion. Twelve healthy volunteers (mean age 35.8 ± 2.8 years) performed graded exercise to exhaustion on a bicycle ergometer in the semisupine position for 8.9 ± 0.9 minutes (maximum work load 900 kg-m/min). Echocardiographic recordings of left ventricular dimensions were obtained continuously and end-expiratory tracings digitized. Heart rate increased from 64 ± 3 to 152 ± 4 beats/min. At peak exercise, end-diastolic diameter increased by 4.52 ± 0.20 cm to 5.24 ± 0.17 cm (p < 0.001), but was unchanged at lower heart rates of 90 and 110 beats/min. End-systolic diameter did not change at any heart rate. Stroke dimension (end-diastolic minus end-systolic diameter) increased from 1.77 ± 0.14 cm to 2.50 ± 0.11 cm (p < 0.005), but was unchanged at lower levels of exercise. Percent shortening in diameter rose from 38.8 ± 1.7% at rest to 48.0 ± 2.1% at peak exercise (p < 0.01), having increased to 43.0 ± 2.5% at 110 beats/min (p < 0.05). Mean velocity of circumferential shortening increased with progressively higher heart rates from its resting value of 5.05 ± 0.49 cm/sec to 9.37 ± 0.77 cm/sec at peak exercise (p < 0.0005). Similarly, velocity of circumferential shortening normalized for end-diastolic diameter increased progressively, from 1.10 ± 0.09 sec−1 at rest to 1.87 ± 0.17 sec−1 at peak exercise (p < 0.0005). Maximal rates of change in diameter and diastolic and, normalized maximum diastolic rate of change all increased progressively and significantly throughout the exercise period.

These results suggest that severe semisupine exertion causes an increase in left ventricular end-diastolic diameter, stroke dimension and percent change in diameter, but no change in end-systolic diameter measured at end-expiration. Increases in indices of left ventricular fiber shortening and rates of lengthening appear earlier in exercise than does an increase in end-diastolic fiber length, suggesting that during lower levels of exertion cardiac output rises primarily by changes in heart rate. The Frank-Starling effect appears, under the conditions of this study, to be reserved for augmenting cardiac performance during severe semisupine exertion.

ADAPTATION OF THE HUMAN HEART to the stress of exercise has long been a subject of intense interest. Although it is well established that cardiac output increases in normal exercising man,1-2 the mechanism by which this increase occurs is still controversial. Cardiac output may increase by augmentation of heart rate or stroke volume. Heart rate is an established mechanism whereby cardiac output increases during exercise in man3,4 and in the dog.5 However, it is not clear how increases in stroke volume occur. End-systolic volume may decrease,6,7 alternatively, end-diastolic volume (the Frank-Starling mechanism) may increase.5,6-10 Although earlier studies suggested the importance of the Frank-Starling mechanism in increasing stroke volume,11-13 Rushmer introduced contradictory evidence14 suggesting that the sole mechanism by which cardiac output increases is by an increase in heart rate. Nevertheless, the studies of Vatner et al.6 in dogs performing maximal exercise indicate a major role for augmentation of stroke volume and end-diastolic volume in increasing cardiac output. Stroke volume likewise increases in exercising man,15-20 but studies provide conflicting evidence regarding changes in end-diastolic volume. Some show variable increases;21 others a decrease;6 and still others, no change.16,22 But these investigations have all used mild-to-moderate exercise levels, when cardiac output might be expected to rise by chronotropic and/or inotropic influences alone. A role for the Frank-Starling mechanism during severe exercise in man has not been established.

Echocardiography provides a method for evaluating left ventricular dimensions continuously during severe exertion, but this technique during exercise has been used only for moderate exercise levels16,23 or the post-exercise state.16,24 Using exercise echocardiography, we studied left ventricular dimensions and indices of contractile function and diastolic lengthening during severe semisupine exercise in normal man. Our study was designed to determine the extent to which the left ventricle uses the Frank-Starling mechanism to augment performance during severe exertion.

Methods

Study Population

The study population consisted of 12 healthy volunteers (10 male and two female) with a mean age of 35.8 ± 2.8 years (range 27-50 years). The subjects et al.8 in dogs performing maximal exercise indicate a major role for augmentation of stroke volume and end-diastolic volume in increasing cardiac output. Stroke volume likewise increases in exercising man,19-20 but studies provide conflicting evidence regarding changes in end-diastolic volume. Some show variable increases;16,21 others a decrease;6 and still others, no change.16,22 But these investigations have all used mild-to-moderate exercise levels, when cardiac output might be expected to rise by chronotropic and/or inotropic influences alone. A role for the Frank-Starling mechanism during severe exercise in man has not been established.

Echocardiography provides a method for evaluating left ventricular dimensions continuously during severe exertion, but this technique during exercise has been used only for moderate exercise levels16,23 or the post-exercise state.16,24 Using exercise echocardiography, we studied left ventricular dimensions and indices of contractile function and diastolic lengthening during severe semisupine exercise in normal man. Our study was designed to determine the extent to which the left ventricle uses the Frank-Starling mechanism to augment performance during severe exertion.

Methods

Study Population

The study population consisted of 12 healthy volunteers (10 male and two female) with a mean age of 35.8 ± 2.8 years (range 27-50 years). The subjects...
were not conditioned athletes. Informed consent was obtained before the exercise protocol. Three other volunteers were excluded from the study because we could not obtain quantifiable simultaneous echocardiographic traces of both sides of the septal endocardium and left ventricular posterior wall at rest or throughout the exercise period.

Exercise Echocardiography

Volunteers exercised in a semisupine position at a 20° head-up-tilt using a mechanically braked bicycle ergometer (Monark model 850). Graded exercise was performed to exhaustion. Subjects pedaled at a constant speed of 18 km/hr. Initial work load was 300 kg-m/min, and was increased by 300 kg-m/min every 3 minutes. The duration of exercise was 8.9 ± 0.9 minutes, and the maximum work load achieved was 900 kg-m/min. Echocardiographic recordings of left ventricular dimensions were obtained at rest and continuously throughout the exercise period. A 2.25 MHz internally focused transducer was hand-held in the standard left parasternal position without the need for special equipment. M-mode recordings were obtained on standard clinical equipment (SK1 Ekoline-20A Echocardiograph interfaced with a Honeywell 1856 Visicorder) and recorded at a paper speed of 100 mm/sec. Systolic blood pressure was determined by auscultation throughout exercise.

Echocardiographic Indices

Echocardiographic indices of left ventricular minor axis dimensions listed below were calculated in all subjects at rest, at heart rates of 90 and 110 beats/min, and at peak exercise. Indices were obtained by digitization of echocardiographic tracings on a standard magnetic digitizing board (Digirgrid, Computer Equipment Corp) using a hand-held planimeter.

We examined the following indices of minor axis dimension: left ventricular end-diastolic diameter (EDD, cm), at the onset of the QRS complex; left ventricular end-systolic diameter (ESD), defined as the minimum minor axis diameter in systole; stroke dimension (SD = EDD - ESD); and percent change in left ventricular minor axis diameter from end-diastole to end-systole (%ΔD = (EDD - ESD/EDD) × 100). The following indices of left ventricular function were also determined: mean velocity of circumferential fiber shortening (Vcf, cm/sec), and this index normalized for EDD (Vcf/EDD, sec⁻¹). We also calculated the following three first derivatives of left ventricular dimensions: maximum rate of decrease in minor axis diameter in systole, and maximum rate of increase of diastolic (max systolic dD/dt and max diastolic dD/dt, cm/sec, respectively); and maximum diastolic rate of increase in diameter normalized for EDD (max diastolic dD/dt/EDD, sec⁻¹). To calculate these derivatives we used a five-point numerical differentiation equation. Time between adjacent digitized points was 2.5 msec. Once the derivative was computed for each value, the derivatives were smoothed by taking an 11-point average of the derivative of the point in question plus 5 on each side of it.

Effects of Respiration

To investigate the possibility that any dimensional changes noted during exercise reflect respiratory variation alone, echocardiograms recorded at rest during normal respiration were compared with records obtained during rapid, deep hyperventilation at rest in six subjects (simulating the respiratory cycle at peak exercise). To minimize the effects of respiration on the echocardiogram, only end-expiratory traces were used in the calculation of indices.

Analysis of Data

For overall analysis of echocardiographic indices, the values of two to four end-expiratory complexes were combined and meaned to give a single value. For statistical analysis the t test of paired values was used. The reproducibility of digitized echocardiographic indices obtained in the resting state as well as validity in reference to angiography for peak rates of wall motion has previously been established by Gibson et al. To assess the reproducibility of digitized data obtained during exercise in terms of inter- and intraobserver variation, a single in-exercise beat was digitized eight times over an 8-day period to minimize the effect of memory by two independent observers. The resulting indices were then subjected to a two-way analysis of variance to assess variation between and within observers for each index. The results of this analysis are shown in table 1. Variance between observers was not significant for most indices. While ESD, SD and %ΔD did demonstrate some interobserver variance, the percentage difference between observers was small (2–5%). No significant variance within observers was noted for any index.

Results

Exercise Echocardiography

Figure 1 shows representative echocardiograms of left ventricular minor axis dimensions at rest and during exercise in one subject. The arrows designate end-diastolic and end-systolic diameters. During exercise, all echoes except those at end-expiration were obliterated by encroachment of lung. This inspiratory obliteration usually occurred within the first 5 minutes of the exercise period.

Left Ventricular Dimensions During Exercise

The effect of exercise on echocardiographic left ventricular dimensions is illustrated in figure 2. Shown here are mean values for EDD, ESD and SD at rest (average heart rate 64 ± 3 beats/min), 90 beats/min, 110 beats/min, and peak exercise (152 ± 4 beats/min). EDD increased 16% at peak exercise, from 4.52 ± 0.20 to 5.24 ± 0.17 cm (mean ± SEM, p < 0.001), but was unchanged at lower heart rates. Similarly, SD increased 43% at peak exercise, from 1.77 ± 0.14 to
Table 1. Reproducibility of Digitizing Method: Two-Way Analysis of Variance

<table>
<thead>
<tr>
<th>Index</th>
<th>Observer*</th>
<th>Variance between observers</th>
<th>Within observers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SEM</td>
<td>%Δ†</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>1</td>
<td>5.31 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.35 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>1</td>
<td>3.35 ± 0.02</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.28 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td>SD (cm)</td>
<td>1</td>
<td>1.96 ± 0.03</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.07 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td>%ΔD</td>
<td>1</td>
<td>36.9 ± 0.5</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>38.7 ± 0.2</td>
<td>—</td>
</tr>
<tr>
<td>VCF/EDD (sec⁻¹)</td>
<td>1</td>
<td>1.08 ± 0.04</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.13 ± 0.02</td>
<td>—</td>
</tr>
<tr>
<td>Max dD/dt (cm/sec)</td>
<td>1</td>
<td>14.24 ± 0.39</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>15.09 ± 0.65</td>
<td>—</td>
</tr>
<tr>
<td>Max -dD/dt (cm/sec)</td>
<td>1</td>
<td>22.00 ± 0.91</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>23.85 ± 0.95</td>
<td>—</td>
</tr>
</tbody>
</table>

*Observers 1 and 2 each digitized same in — exercise complex eight times for comparison between and within observers.
†Percent difference between means.
Abbreviations: EDD = end-diastolic diameter; ESD = end-systolic diameter; SD = stroke dimension; %ΔD = percent shortening in diameter; VCF/EDD, normalized mean velocity of circumferential shortening; max dD/dt = maximum rate of decrease in diameter, systole; max - dD/dt = maximum rate of increase in diameter, diastole.

2.50 ± 0.11 cm (p < 0.005) with no significant change at lower heart rates. In contrast, ESD did not change significantly from rest to any level of exercise.

The effect of exercise on %ΔD is illustrated in figure 3, panel A. At rest, %ΔD averaged 38.8 ± 1.7 and at peak exercise rose to 48.0 ± 2.1 (p < 0.01), having increased at 110 beats/min to 43 ± 2.5 (p < 0.05).

Figure 3, panels B–D illustrate the influence of exer-

![Echocardiogram of a representative subject at rest (top panel) and during exercise (bottom panel). During severe exercise all echoes except those at end-expiration are frequently obliterated by encroachment of lung. Arrows designate end-diastolic and end-systolic diameters. Bottom panel is reduced in size to accommodate more complexes for illustration of respiratory variation.](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.CIR.65.4.657/-/DC1/fig-1)

Figure 1.
exercise on indices of left ventricular velocity of shortening. Mean Vcf at rest (panel B) was 5.05 ± 0.49 cm/sec. This index increased progressively at higher heart rates: 6.48 ± 0.72 cm/sec at 90 beats/min (p < 0.02); 7.04 ± 0.55 cm/sec at 110 beats/min (p < 0.001); and 9.37 ± 0.77 cm/sec at peak exercise (an 86% increase) (p < 0.0005). Similarly, Vcf/EDD increased 70% from its resting value of 1.10 ± 0.09 sec\(^{-1}\) to a peak value at peak exercise of 1.87 ± 0.17 sec\(^{-1}\) (p < 0.0005). During submaximal heart rates, there were progressive and significant changes at 90 beats/min (1.42 ± 0.17 sec\(^{-1}\), p < 0.05), and at 110 beats/min (1.56 ± 0.14 sec\(^{-1}\), p < 0.005). Max systolic dD/dt (panel D) also increased substantially (51%) from its resting value of 11.12 ± 1.11 cm/sec to 16.76 ± 1.75 cm/sec at peak exercise (p < 0.01), showing progressive increases at the lower heart rates of 90 beats/min (13.11 ± 1.15, p < 0.01) and 110 beats/min (14.32 ± 1.06, p < 0.02), respectively.

The effect of exercise on the derived rates of increase in diastolic left ventricular diameter, max diastolic dD/dt and max diastolic dD/dt/EDD, is shown in figure 4. Both indices showed stepwise increases at progressively higher heart rates. Panel A shows max diastolic dD/dt increasing progressively at all levels of exercise from its resting value of 3.53 ± 0.38 cm/sec to 7.48 ± 1.06 cm/sec at 90 beats/min (p < 0.01), 10.08 ± 1.03 cm/sec at 110 beats/min (p < 0.001), and 12.99 ± 0.98 cm/sec at peak exercise (p < 0.0001). The latter value is a 268% increase over the rest value. A similar, nearly linear, increase in max diastolic dD/dt/EDD was noted. At rest, the mean value was 0.77 ± 0.08 sec\(^{-1}\); at 90 beats/min, 1.56 ± 0.14 sec\(^{-1}\) (p < 0.02); at 110 beats/min, 2.17 ± 0.17 sec\(^{-1}\) (p < 0.0005); and at peak exercise, 2.53 ± 0.13 sec\(^{-1}\) (p < 0.0001), a 229% increase over that at rest.

**Effect of Respiration**

To investigate the possibility that the dimensional changes seen at exercise were in part caused by respiratory variation, we studied the effects of altering the depth of respiration in six resting subjects, comparing the effect of normal respiration with rapid hyperventilation on resting EDD. During normal respiration, the end-expiratory EDD of 5 ± 0.08 cm was significantly greater than the end-inspiratory EDD of 4.24 ± 0.10 cm (p < 0.02). However, rapid, deep hyperventilation at rest, simulating respiration at peak exercise, resulted in no greater increase in EDD at end-expiration (4.98 ± 0.09 cm, NS); end-inspiratory echoes were generally obliterated (fig. 1, lower panel). These results indicate that the dimensional changes seen at exercise were probably not caused by respiratory variation alone.

**Systolic Blood Pressure**

Systolic blood pressure, determined by auscultation, increased progressively and substantially throughout exercise from its resting value of 119 ± 4 mm Hg to 151 ± 5 mm Hg at 90 beats/min (p < 0.001); 179 ± 7 mm Hg at 110 beats/min (p < 0.001); and 192 ± 7 mm Hg at peak exercise (p < 0.001). Systolic blood pressure at peak exercise also differed significantly from its level at 110 beats/min (p < 0.01).

**Discussion**

The mechanism by which the heart adapts to the demands of severe exercise is controversial. Many have thought that end-diastolic volume must increase in man during severe exercise, since stroke volume increases.**6-10** While some studies suggest that EDD in-
creases in exercising man,\textsuperscript{10, 21} others have reported that angiographically measured end-diastolic volume or dimension either remains constant or diminishes.\textsuperscript{8, 14, 16, 22} In a recent echocardiographic study EDD likewise remained unchanged during mild exercise but increased above resting levels during recovery.\textsuperscript{16} However, these studies have all used mild-to-moderate exercise levels, when heart rate increases and/or inotropic influences alone may increase cardiac output.\textsuperscript{22} No prior study in man has used severe stress in the direct evaluation of dimensional changes in the left ventricular cavity during exercise. Studies of left ventricular dimensions involving severe or maximal exertion have usually been limited to animals. The early canine studies of Wilson\textsuperscript{82} and of Wildenthal and Mitchell\textsuperscript{82} both demonstrated increases in EDD that occur with severe exertion. The studies of Vatner et al.\textsuperscript{8} and Horwitz et al.\textsuperscript{8} likewise indicate significant increases in left ventricular EDD at the time of, but not before, maximal exercise. These investigations therefore provide clear evidence of the utilization of the Frank-Starling mechanism during severe exertion. It should be noted that in the latter two studies the increases in EDD, though significant, were relatively small when compared with the present study. Recognizing the important influence of the pericardium on diastolic left ventricular function,\textsuperscript{83} one might speculate that some postoperative pericardial restriction in these animals partly accounts for the decrease in these changes in diameter.

Our study is evidence that the Frank-Starling mechanism contributes to the adaptation of the human heart to severe semisupine exercise, shown by a significant increase in left ventricular EDD. Diastolic dimension remained unchanged at lower levels of exercise. At peak exercise our subjects also had substantial increases in SD, an index of stroke volume, and percent change in diameter, an index of ejection fraction. The increase in SD appears in our subjects to be due primarily to an increase in EDD, since ESD did not decrease.

Previous studies of the effect of exercise on ESD or volume provide disparate results. In maximally exercising dogs, Vatner et al.\textsuperscript{8} report a decrease in ESD, while Horwitz et al.\textsuperscript{8} report no change in this index. Whereas in submaximally exercising man this index has previously been found to diminish slightly\textsuperscript{8, 17} or remain constant,\textsuperscript{16} in the present study ESD did not change significantly at any level of exercise.
In our subjects, indices of left ventricular shortening velocity and rate of fiber lengthening increased during exercise at lower heart rates than did the dimensional changes. These data support the hypothesis that during submaximal exertion cardiac output rises without the Frank-Starling mechanism and instead depends on inotropic and chronotropic influences. The substantial augmentations in both Vcf and Vcf/EDD are consistent with the echocardiographic data of Hirshleifer et al.\textsuperscript{25} in subjects evaluated during atropine-induced tachycardia. Similar changes have also been noted during maximal\textsuperscript{27} and submaximal\textsuperscript{19} exercise in postoperative patients studied fluoroscopically with implanted radiopaque markers. Hirshleifer et al.\textsuperscript{25} found a fall in normalized Vcf during atropine-induced tachycardia when phenylephrine was added to raise systemic blood pressure (consistent with the force-velocity relationship). In contrast, at higher heart rates but before changes in left ventricular dimensions, our subjects showed increases in Vcf and Vcf/EDD despite accompanying elevations in systolic blood pressure, suggesting early increases in contractility during exercise.

Max systolic dD/dt increased markedly during peak exercise (fig. 3), as well as at lower heart rates. Echocardiographically determined systolic dD/dt has been found previously to correlate well with the same index determined angiographically in patients at rest\textsuperscript{27} and during moderate exercise,\textsuperscript{21} in exercising dogs,\textsuperscript{6} and with maximum dP/dt in man determined at catheterization.\textsuperscript{35}

In our subjects, max diastolic dD/dt and max diastolic dD/dt/EDD bore a close relationship to exercise-induced increases in heart rate (fig. 4). These findings are in agreement with the previous studies in humans of Galbo et al.\textsuperscript{19} These diastolic indices change more than measures of systolic contractile function, suggesting usefulness in future exercise evaluations of diseased ventricles.

Echocardiography has not previously been used to examine left ventricular wall motion during severe or maximal exercise. Kraunz and Kennedy\textsuperscript{24} studied left ventricular wall motion at rest and immediately after, but not during, moderate exercise. While Fogelman et al.\textsuperscript{28} recorded echocardiograms during moderate exercise, their investigations were limited to the study of posterior left ventricular endocardial velocity. Stein et al.\textsuperscript{16} recently assessed left ventricular dimensions during and after moderate, but not severe, exercise.

Most exercise protocols use upright exercise on a bicycle or treadmill. It was extremely difficult for us to record reproducible echocardiograms during exercise in the sitting position, and we had much better success in obtaining data during semisupine exercise. A number of previous studies indicate that the supine position results in a somewhat greater EDD relative to the upright position.\textsuperscript{15, 31, 32, 34} In the face of such an expected increase in resting EDD in our subjects, EDD rose even higher during severe exercise, a finding consonant with the earlier canine studies of Wilson.\textsuperscript{35}

Obtaining a clear in-exercise echocardiogram poses several technical problems. First, we could not obtain high-quality in-exercise echocardiograms in the upright position. Second, exaggerated chest wall movement attending exercise-induced hyperventilation often introduces considerable lung artifact during deep inspiration, obscuring the echocardiogram during this phase of respiration (fig. 1, bottom panel). However, during the expiratory phase the echocardiogram is usually adequate. To eliminate the possible effects of respiratory variation of the echocardiogram, only end-expiratory traces were used in our calculations. We found that during normal respiration echocardiographic end-diastolic left ventricular minor axis diameter was greatest at end-expiration and least at end-inspiration; this agrees with the recent study of Brenner and Waugh.\textsuperscript{29} These observations prompted us to examine the effects of rapid, deep hyperventilation at rest, simulating respiration at peak exercise, which resulted in no greater increase in EDD at end-expiration; end-inspiratory echoes were generally obliterated. Thus, dimensional changes seen during exercise were not caused by respiratory variation alone. Whether the Frank-Starling effect is evidenced as strongly during phases of the respiratory cycle other than end-expiration remains uncertain due to the technical limitations inherent in measuring left ventricular dimensions in exercise during these other phases.

In summary, during severe semisupine exertion the human left ventricle exhibits increased EDD, SD and fractional change in diameter, without a change in ESD, measured at end-expiration. Increases in indices of left ventricular shortening velocity and diastolic fiber lengthening appear earlier in exercise than do dimensional changes, suggesting that during submaximal exertion cardiac output can rise by heart rate in the absence of the Frank-Starling mechanism. The Frank-Starling effect appears under the experimental conditions of this study to be reserved for augmenting cardiac performance only during severe exertion.

Acknowledgments

We gratefully acknowledge the assistance of Roy Prouse and Bruce Blum of The Johns Hopkins University Applied Physics Laboratory in the development of the digitizing programs, and Spring Forsythe in the preparation of the manuscript.

References

Evidence of frank-starling effect in man during severe semisupine exercise.
J L Weiss, M L Weisfeldt, S J Mason, J B Garrison, S V Livengood and N J Fortuin

Circulation. 1979;59:655-661
doi: 10.1161/01.CIR.59.4.655

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/59/4/655.citation