Echocardiographic Measurements in Normal Subjects from Infancy to Old Age

WALTER L. HENRY, M.D., JULIUS M. GARDIN, M.D., AND JAMES H. WARE, PH.D.

SUMMARY  Echocardiographic data from 92 younger normal subjects (1 month to 23 years of age) and 136 older normal subjects (20–97 years of age) were pooled and analyzed to obtain prediction equations for normal echocardiographic values. Using a bivariate regression model with the assumption that variability is constant as a percentage of the expected value, we developed regression equations and graphs that allow calculation of a 95% prediction interval for several echocardiographic measurements as a function of the subject’s age and either body weight or body surface area. Body weight could be substituted for body surface area with no loss of precision. Further, examination of residuals showed that the linear prediction model fit well for all ages and all echocardiographic measurements studied. The measurements were obtained using the recently published standards recommended by the American Society of Echocardiography.

WE RECENTLY ANALYZED our experience with M-mode echocardiography in two groups of normal subjects.1,2 One group consisted of boys and girls who ranged from 1 day to 23 years of age and the other consisted of men and women ages 20–97 years. After these data had been analyzed, the American Society of Echocardiography recommended measurement standards for M-mode echocardiography3 that differed in some respects from those we used to construct the normal graphs based on our previous studies of normal subjects.

To generate normal values for echocardiographic measurements based on the new American Society of Echocardiography standards, we reanalyzed the data from the younger and older normal subjects. The new regression equations and graphs derived from this analysis are applicable to subjects of any age and have been related to both body surface area and body weight. The development of normal data based on body weight simplifies the determination of normal values because it eliminates the intermediate step of calculating body surface area.

Methods

Study Population

Two groups of normal subjects were studied. One group consisted of 92 normal subjects 1 month to 23 years of age.1 Forty-five of the 92 were males and 47 were females. No subject had evidence of heart or systemic diseases. Twelve-lead ECGs and cuff blood pressure measurements were available in most patients and were found to be normal.

The other group consisted of 136 adult normal subjects (78 men and 58 women) ages 20–97 years.2 No subject had a history of heart disease or hypertension, and all subjects had a normal physical examination, ECG and chest x-ray. No subject was more than 25% above or below the desirable body weight set forth by the Metropolitan Life Insurance Company.4 Also, no subject had echocardiographic evidence of pericardial effusion or valvular heart disease, including mitral valve prolapse.

Echocardiographic Measurements

These were made from M-mode echocardiograms. Each subject was studied in the supine and left lateral decubitus position. Studies were performed using either an Ekoline 20A or a Hoffrel 201 transceiver interfaced to a Honeywell 1856 strip-chart recorder. A 2.25-MHz, 1.25-cm diameter, unfocused Aerotech transducer was used in the oldest children and adults, a 3.5-MHz, 1.25-cm diameter transducer was used in the young children, and a 5.0-MHz, 0.6-cm diameter transducer was used in infants and very small children.

Measurements were made according to the recommendations of the American Society of Echocardiography5 (fig. 1). The internal dimension of the left ventricle at end-diastole was measured at the onset of the QRS complex, and the end-systolic dimension was measured at the nadir of septal motion (i.e., when the ventricular septum was farthest from the anterior chest wall). Both measurements were made using the T-scan technique with the ultrasound beam passing through the left ventricle slightly caudal to the tip of the mitral valve.6

The thicknesses of the ventricular septum and posterior wall were measured in the same portion of the record used to measure the left ventricular internal dimensions.3 Measurements were made at the onset of the QRS complex using the switched-gain circuit.6 Aortic root and left atrial dimensions were recorded by angling the ultrasound beam from the mitral valve into the aortic root.7 Minor adjustments of transducer orientation were made until the ultrasound beam was reflected from the aortic valve leaflets. The aortic root dimension was measured at end-diastole at the onset of the QRS complex, and the left atrium was measured at its maximum dimension at end-systole.3 The posterior wall of the left atrium was identified with the switched-gain circuit.6

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ECHO MEASUREMENTS IN NORMAL SUBJECTS/Henry et al. 1055

METHODS OF MEASUREMENT

NORMAL DATA

EKG

LEFT VENTRICULAR DIMENSIONS

LVDD(D) = left ventricular dimension at end-diastole; LVDD(S) = left ventricular dimension at end-systole; ST(D) = ventricular septal thickness at end-diastole; ST(S) = ventricular septal thickness at end-systole; PWT(D) = left ventricular posterior wall thickness at end-diastole; PWT(S) = left ventricular posterior wall thickness at end-systole; AO = aortic root dimension at end-diastole; LA = maximal left atrial dimension.

All 136 adult subjects and 72 of the 92 younger subjects (78%) had a lead II ECG recorded simultaneously with the echocardiogram. Therefore, measurements of left ventricular end-diastolic dimension, septal and posterior wall thickness, and aortic root dimension were obtained in these 208 subjects. Left atrial dimension and left ventricular end-systolic dimension were measured in all 228 subjects.

Measurements were made using the leading-edge method recommended by the American Society of Echocardiography. In this method, the lines on the M-mode echocardiogram that represented the structures being measured were identified and measurements were made from the front edge (i.e., the most anterior surface) of these lines. Three consecutive measurements were made and averaged.

The closing velocity of the tip of the anterior leaflet of the mitral valve in early diastole (EF slope) was also measured. This measurement was made in the portion of the record in which both anterior and posterior leaflets were seen and the excursion of the anterior mitral leaflet was maximal. The EF slope (and not EFc) was used in the study. The American Society of Echocardiography did not make recommendations for this measurement.

In addition to the primary measurements, several derived descriptors of left ventricular size and function were computed. Left ventricular volumes at end-diastole and end-systole were estimated, and ejection fraction was calculated using the cubed assumption. The percentage of left ventricular fractional shortening was also computed.

Statistical Analysis

Pooled data from all subjects were analyzed. Each echocardiographic measurement was fitted to a bivariate regression model with age and a transformation of either body surface area or weight as the independent variables. Because prior studies have shown that measurements were either not or only minimally influenced by sex differences, the sex of the subject was not included in the regression model.

In the previous study of younger normal subjects, the various echocardiographic measurements could be related to body surface area by the general regression model M = B(ASA)^k + A, in which M is the echocardiographic measurement, B is the slope of the regression equation, ASA is body surface area, A is the intercept, and R is equal to 1, 1/2 or 1/3, corresponding to body surface area or its square or cube root. The need for such root transformations was shown graphically. Moreover, these root transformations also increased the regression sum of squares, a measure of the fit of the regression model. The left ventricular internal dimensions at end-diastole and end-systole, aortic root dimension, left atrial dimension, and mitral EF slope were all linearly related to the cube root of body surface area. Ventricular septal thickness and left ventricular posterior wall thickness varied linearly with the square root of body surface area. It was also shown in that analysis that the regression model was improved by the assumption that the variability (standard deviation) of the echocardiographic measurement at a given body surface area is proportional to the predicted value. We used the same approach in this analysis.

In the adult normal study, these same echocardiographic measurements were found to be affected by age. However, when subjects were grouped by age, the slope of the regression of these measurements on body surface area did not vary significantly between age groups. Analysis of the variation in the intercept of the regression with age indicated that the effect of age could be closely approximated by a linear regression on age. In the present study, therefore, we used a
bivariate regression model of the form
\[ M = B(BSA)^n + C(AGE) + A. \]

We further assumed that the standard deviation of observed values for a given age and body surface area is proportional to their predicted value. Thus, the 95% prediction limits are given by \( E(M) \pm 2 \cdot \hat{P} \cdot E(M) \), where \( E(M) \) is the predicted value of \( M \) at a specified age and body surface area or weight and \( P \) is the standard deviation of the data expressed as a percent. The assumption of proportional fitting required the use of iterative methods for estimating the regression parameters. Although the assumption of proportional variability had not been previously used for analyzing normal adults, the distinction proved to be insignificant because of the relatively small variation in heart size in adults compared with children.

Left ventricular fractional shortening and ejection fraction were independent of both body surface area and age. Therefore, these derived measurements were expressed simply as a mean value and a 95% prediction interval.

To derive regression equations based on body weight, we first examined the relation between body weight and body surface area in the pooled normal data. Body surface area (BSA) and weight (WT) were assumed to be related by the equation \( BSA = K(WT)^X \), where \( K \) is a constant and \( X \) is a power. An iterative computer program was used to determine the value of \( X \) that produced the best fit to the data. After the values of \( K \) and \( X \) were determined, the equation relating body surface area and weight was substituted into the general regression equation based on body surface area. As a result, the general regression equation based on body weight was \( M = B(K \cdot WT)^{\frac{n}{X}} + C(AGE) + A. \)

**Results**

**Relation Between Body Weight and Body Surface Area**

Using the pooled normal data, body weight was found to be related to body surface area by the equation \( BSA = 0.12(WT)^{0.84} \). The correlation of the two values was extremely high (\( r = 0.999 \)). Therefore, substitution of the appropriate function of body weight for body surface area affected the regression analysis negligibly.

**Analysis of Pooled Data**

The regression equations derived from pooled data of the younger and older normal subjects are summarized in tables 1 and 2. Equations are given for each of the primary and derived measurements and are expressed both as a function of body surface area and age (table 1), as well as of body weight and age (table 2).

To assess whether the equations based on body weight would result in values equivalent to those generated by equations using body surface area,

<p>| TABLE 1. Equations for Predicting Normal Echocardiographic Measurements from Body Surface Area and Age |
|-----------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Measurements</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic dimension*</td>
<td>45.3 (BSA)^{1/3} - 0.03 (AGE) - 7.2 ± 12%</td>
</tr>
<tr>
<td>LV end-systolic dimension*</td>
<td>28.8 (BSA)^{1/3} - 0.03 (AGE) - 4.1 ± 18%</td>
</tr>
<tr>
<td>Septal thickness*</td>
<td>5.44 (BSA)^{1/9} + 0.03 (AGE) + 1.5 ± 18%</td>
</tr>
<tr>
<td>LV free wall thickness*</td>
<td>5.56 (BSA)^{1/9} + 0.03 (AGE) + 1.1 ± 16%</td>
</tr>
<tr>
<td>Aortic root dimension*</td>
<td>24.0 (BSA)^{1/9} + 0.1 (AGE) - 4.3 ± 18%</td>
</tr>
<tr>
<td>Left atrial dimension*</td>
<td>28.5 (BSA)^{1/9} + 0.08 (AGE) - 0.9 ± 18%</td>
</tr>
<tr>
<td>Mitral EF slope*</td>
<td>161 (BSA)^{1/9} - 0.9 (AGE) - 36 ± 45%</td>
</tr>
</tbody>
</table>

*Measurements made according to standards recommended by the American Society of Echocardiography. In these equations, body surface area (BSA) is expressed in square meters, age in years, dimensions and thicknesses in millimeters, and EF slope in millimeters per second.

<p>| TABLE 2. Equations for Predicting Normal Echocardiographic Measurements from Body Weight and Age |
|-----------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic dimension*</td>
<td>22.4 (WT)^{0.211} - 0.03 (AGE) - 7.2 ± 12%</td>
</tr>
<tr>
<td>LV end-systolic dimension*</td>
<td>14.2 (WT)^{0.211} - 0.03 (AGE) - 4.1 ± 18%</td>
</tr>
<tr>
<td>Septal thickness*</td>
<td>1.88 (WT)^{0.32} + 0.03 (AGE) + 1.5 ± 18%</td>
</tr>
<tr>
<td>LV free wall thickness*</td>
<td>1.92 (WT)^{0.32} + 0.03 (AGE) + 1.1 ± 16%</td>
</tr>
<tr>
<td>Aortic root dimension*</td>
<td>11.8 (WT)^{0.211} + 0.1 (AGE) - 4.3 ± 18%</td>
</tr>
<tr>
<td>Left atrial dimension*</td>
<td>14.1 (WT)^{0.211} + 0.08 (AGE) - 0.9 ± 18%</td>
</tr>
<tr>
<td>Mitral EF slope*</td>
<td>79.4 (WT)^{0.211} - 0.9 (AGE) - 36 ± 45%</td>
</tr>
</tbody>
</table>

*Measurements made according to standards recommended by the American Society of Echocardiography. In these equations, body weight (WT) is expressed in kilograms, age in years, dimensions and thicknesses in millimeters, and EF slope in millimeters per second.
values computed from the two equations were compared. The comparison involved using both the body surface area equations and the body weight equations to compute the expected value of each measurement for each of the normal subjects analyzed in the present study. The two expected values, one computed from the body surface area and the other from body weight, were then compared. Of the primary echocardiographic measurements, the two expected values were within 3% of each other in over 99% of the patients. The maximum difference between the two

values was 5%. The only exception was mitral EF slope, in which 92% of patients had expected values that were within 3% of each other.

Comparison of Pooled Equations with Previous Equations

The equations derived in the present study using the pooled data were compared to the regression equations that previously had been derived separately from the normal data derived from younger subjects and adults. In all younger normal subjects, the values derived by the present and previous equations were within 5% of each other for each of the primary echocardiographic measurements, and the average difference was typically 1%. In the older normal subjects, the two derived values were within 5% of each other in over 97% of patients.

FIGURE 2. Left ventricular (LV) dimension at end-diastole (vertical axis) plotted against body surface area (BSA) (lower horizontal axis) and body weight (upper horizontal axis). This echocardiographic measurement was made according to standards recommended by the American Society of Echocardiography (A.S.E.). The two diverging dark solid lines that extend from a BSA of 0.2 m² to a BSA of 2.3 m² represent the 95% prediction intervals of measurements obtained in normal subjects from 30 days to 20 years of age. The 95% prediction intervals for adult subjects who are either 50 or 80 years of age are indicated by the dark solid lines that extend from a BSA of 1.4 m² to a BSA of 2.3 m².

FIGURE 3. Left ventricular (LV) dimension at end-systole (vertical axis) plotted against body surface area (BSA) and body weight (horizontal axes). See legend to figure 2 for abbreviations and description of this figure.
FIGURE 4. Ventricular septal thickness plotted against body surface area (BSA) (lower horizontal axis) and body weight (upper horizontal axis). This echocardiographic measurement was made according to standards recommended by the American Society of Echocardiography (A.S.E.). The two diverging dark solid lines that extend from a BSA of 0.2 m² to a BSA of 2.3 m² represent the 95% prediction intervals of measurements obtained in normal subjects from 30 days to 20 years of age. The 95% prediction intervals for adult subjects who are 40, 60 and 80 years of age are indicated by the dark solid lines that extend from a BSA of 1.4 m² to a BSA of 2.3 m².

Normal Data Graphs

The regression equations derived in the present study were used to construct graphs that summarize the echocardiographic data from our normal subjects. Each graph was constructed by plotting the echocardiographic measurement on the vertical axis in a linear fashion. Body surface area was indicated on the lower horizontal axis and body weight on the upper horizontal axis. The horizontal axes were expressed by the same mathematical function used in the regression equations. For example, left ventricular end-diastolic dimension was expressed as a cube root function of body surface area, while body weight was plotted on an axis that displayed weight to the (0.64/3) power.

The graphs relating the primary and derived echocardiographic measurements are shown in figures 2–8. Left ventricular fractional shortening and ejection fraction were independent of body surface area and age. The percentage of fractional shortening averaged 36%, with a 95% percent confidence limit of 28–44%. Ejection fraction averaged 74%, with a 95% prediction interval of 64–83%.

Discussion

The regression equations and graphs in the present report are a refinement of our previously analyzed normal data. This refinement results in several ad-
vantages. First, the new regression equations are generally applicable to subjects of any age because they were derived from subjects 1 month to 97 years of age. Although the study of older normal subjects contained a small number of women older than 70 years of age, subsequent echocardiographic studies of additional women in this age group indicate that having only a small number of elderly women does not influence our results. This experience is consistent with our previous observation that sex differences had little or no impact on echocardiographic measurements. Therefore, we combined the data from our two previous studies without regard to sex differences and made a number of simplifying assumptions to derive these new equations. This approach seems reasonable because the values derived from the new and older equations are nearly identical.

A second advantage of the new equations and graphs is the use of body weight as well as body surface area. The use of body weight to account for the size of the subject simplifies calculation of the predicted echocardiographic value because it eliminates the need to determine body surface area from height and weight. In normal subjects whose weight fell within 25% of desirable body weight, the regression equations based on either body weight or body surface area resulted in nearly identical calculated echocardiographic values. At present, it is not clear which of the two regression equations to use in patients whose weight or height fall well outside the normal range (i.e., obese or underweight patients, very tall or very short subjects).

A third advantage of the new equations and graphs...
Figure 8. Mitral EF slope (vertical axis) plotted against body surface area (BSA) and body weight (horizontal axes). The American Society of Echocardiography has not recommended standards for this measurement. See legend to figure 4 for abbreviations and description of this figure.

is that they were derived using the standards recommended by the American Society of Echocardiography. It is hoped that standardization of echocardiographic measurements will facilitate comparison of data from different laboratories. The availability of normal data based on these new standards may further aid these comparisons.

Several recent clinical studies of large patient groups have indicated the utility of these regression equations. Because body size and age of the patients evaluated in these studies varied widely, the age and body surface area (or weight) of each patient was used with the appropriate regression equation to calculate the predicted value for a given measurement from each patient. The predicted value was subtracted from the actual measured value and the difference was divided by the predicted value. Thus, it was possible to express the measured value as a percentage of the predicted value. Because 95% of measurements in normal subjects fall within a specific percentage of the mean (or predicted value), it was possible to use the calculated percent predicted value to determine whether the measurement fell within the 95% prediction interval for normal subjects. For example, 95% of left ventricular free wall thickness measurements in normal subjects fall within 16% of the mean value. Therefore, if a measured left ventricular free wall thickness in a patient with aortic stenosis was 28% greater than the value predicted from the patient’s age and body surface area (or weight), we concluded that the wall was thickened. Likewise, if the mean of all the percent predicted values of left ventricular free wall thickness for the entire patient population was computed and found to be statistically greater than zero, we concluded that as a group, the left ventricular free wall was thickened. It seems likely that this type of analysis will prove useful in future studies of patients with heart disease.

Although accurate quantification of echocardiographic measurements is subject to many methodologic pitfalls, it is a desirable goal in the clinical diagnosis of heart disease and the study of the pathophysiology of these diseases. Because body size and age have an important influence on echocardiographic measurements, quantification should be improved by accounting for these factors.

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Echocardiographic Determination of Contraction and Relaxation Measurements of the Left Ventricular Wall in Normal Subjects and Patients with Muscular Dystrophy

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SUMMARY Boys with Duchenne’s muscular dystrophy (DMD) usually have a cardiomyopathy characterized by fibrosis of the epicardial half of the left ventricle. This cardiomyopathy is difficult to detect by noninvasive techniques. We report a technique that evaluates incremental left ventricular posterior wall thickening and thinning. High-quality left ventricular posterior wall echoes in 24 boys with DMD and 32 controls were recorded at chordal level two times 1 year apart. Endocardial and epicardial echoes and a timing ECG were digitized and analyzed by minicomputer. Left ventricular wall amplitudes were determined at standardized temporal increments during contraction and relaxation. To compare with this left ventricular assessment technique, systolic ejection times, shortening fraction and mean velocity of circumferential fiber shortening (Vcf) were also computed in the standard way. Mean year-to-year changes were minimal. Mean Vcf, the ratio of prejection period to left ventricular ejection time and shortening fraction during the first year were statistically similar to those of the controls. Shortening fraction decreased slightly during the second year and became significantly different from the control, but remained within the normal range. Left ventricular wall thickness and cavity size were significantly less in boys with DMD than in controls. Therefore, we had to normalize incremental wall thickness to determine if any significant difference occurred. To do this, we evaluated the percentage of maximal wall thickness which occurred at a given percent of systole and diastole. Using this technique, it was shown that thickening during systole was a nearly linear process with respect to time in both groups. However, relaxation was significantly different between the groups. Relaxation was found to be an a linear process, and most thinning occurred in the first 40% of diastole. The major finding of this investigation was that the left ventricular wall of boys with DMD thinned at a slower rate than that of normal subjects. This new technique appears to be sensitive and demonstrates subtle changes in the left ventricular posterior wall.

THE CARDIAC PATHOLOGY of Duchenne’s muscular dystrophy (DMD) has been described in only a few patients. Detailed gross and microscopic analyses of 15 hearts of affected boys showed that left ventricular fibrosis and/or dilation was present in 94%. The results (table 1) indicate that left ventricular fibrosis was usually localized to the epicardial half of the left ventricular free wall and usually occurred in a diffuse distribution. In 27%, fibrotic changes were localized to the posterior basal area of the heart. The fibrosis is not similar to that observed in myocardial infarction, for in DMD, normal muscle cells are intermixed with fibrotic areas.

Although death in some patients with DMD results from congestive cardiac failure, frank cardiac decompensation is a relatively uncommon feature in the early or middle stage of the disease. However, electrocardiographic evidence of cardiac abnormality is frequently found in children younger than 5 years of age. Thus, DMD provides a model of mild cardiomyopathy that progresses to a more severe form in the second decade.

The purpose of our investigation was to develop a method for evaluating the cardiomyopathy found in DMD patients. Previous investigations have shown that conventional echocardiographic measurements of myocardial function, such as velocity of circumferential fiber shortening (Vcf), shortening fraction, ejection fraction and stroke index, have been normal or...
Echocardiographic measurements in normal subjects from infancy to old age.
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