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Normal values of regional left ventricular endocardial motion: multicenter color kinesis study

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Mor-Avi, Victor, Kirk Spencer, John Gorcsan, Anthony Demaria, Thomas Kimball, Mark Monaghan, Julio Perez, Jing Ping Sun, Lynn Weinert, James Bednarz, Keith Collins, Kathy Edelman, Oi Ling Kwan, Betty Glascock, Jane Hancock, Chris Baumann, James Thomas, and Roberto Lang. Normal values of regional left ventricular endocardial motion: multicenter color kinesis study. *Am J Physiol Heart Circ Physiol* 279: H2464–H2476, 2000.—Our goal was to establish normal values for quantitative color kinesis indexes of left ventricular (LV) wall motion over a wide range of ages, which are required for objective diagnosis of regional systolic and diastolic dysfunction. Color-encoded images were obtained in 194 normal subjects (95 males, 99 females, age 2 mo to 79 yr) in four standard views. Quantitative indexes of magnitude and timing of systolic and diastolic function were studied for age- and gender-related differences. Normal limits of all ejection and filling indexes were in a narrow range (≤25% of the mean), with no major gender-related differences. Despite invariable ejection fractions, both peak filling and ejection rates decreased with age (30 and 20%, correspondingly) with a concomitant increase in mean filling and ejection times, resulting in five- and twofold increases in the late to early filling and ejection ratios, correspondingly. Diastolic asynchrony increased with age (from 4.7 ± 2.0 to 6.4 ± 3.2 from the 2nd to 7th decade). The normal values of color kinesis indexes should allow objective detection of regional LV systolic and diastolic dysfunction.

echocardiography; ultrasound imaging; ventricular function; wall motion

COLOR KINESIS IS AN EMERGING echocardiographic technique based on acoustic quantification, which uses color-encoding to depict left ventricular (LV) systolic and diastolic endocardial motion (27, 28, 39, 43, 45). We have previously described a method of quantitative segmental analysis of color kinesis images (31), which allowed us to accurately detect resting wall motion abnormalities in patients with coronary heart disease (27). More recently, this technique was extended to automatically detect stress-induced wall motion abnormalities by analyzing systolic color kinesis images obtained during dobutamine stress testing (25). Analysis of diastolic color kinesis images proved useful for objective assessment of LV diastolic dysfunction in patients with LV hypertrophy (44), as well as regional LV filling abnormalities in patients with dilated cardiomyopathy and severe mitral regurgitation (19).

However, a new technique, which detects abnormalities by comparing individual patient's data with normal values, relies on having these normal values established in a large sample of the normal population. Accordingly, normal values of different indexes of magnitude and timing of global and regional LV function derived from color kinesis images need to be established to allow objective detection of abnormalities with a high level of confidence. We also hypothesized that these indexes may be age and gender dependent, in which case normal values would need to be established for different demographic groups. Accordingly, the purpose of this collaborative multicenter effort was to establish normal values for magnitude and timing indexes of wall motion by acquiring and analyzing systolic and diastolic color kinesis images in a large group of normal subjects of both sexes over a wide range of ages.

METHODS

Study population. The protocol for this study was approved by the Institutional Review Board of the University of Chicago (protocol #9171). This protocol was initially designed to include eight age groups (8 decades between 0 and 80 yr) with a minimum of 20 normal subjects each (50% males and 50%

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females). Inclusion criteria were *1*) absence of cardiovascular disease, including systemic hypertension, coronary artery disease, valvular heart disease, and diabetes; *2*) normal systolic function (ejection fraction >50% calculated using manual tracings with method of disks), with no evidence of wall motion abnormalities; *3*) normal sinus rhythm with resting heart rate between 55 and 95 beats/min (above age 5) and no left bundle branch block; *4*) normal blood pressure (systolic <145 and diastolic <90 mmHg); *5*) no more than mild mitral or tricuspid regurgitation and no more than trivial aortic regurgitation (all graded using a standard, color Doppler-based, subjective scale, including trivial, mild, moderate, and severe regurgitation); *6*) no evidence of left ventricular hypertrophy; and *7*) echocardiographic image quality adequate for automated border detection and tracking by acoustic quantification system (6). On the basis of these criteria, 194 normal subjects (95 males, 99 females, age 2 mo to 80 yr) were enrolled in the protocol.

Image acquisition. Echocardiographic images were acquired in the parasternal short and long axis as well as apical four- and two-chamber views using a 2.5- or 3.5-MHz transducer (SONOS 2500, Hewlett-Packard) with the subject in the left lateral decubitus position. Parasternal short-axis views were obtained at the level of the tips of the papillary muscles. Parasternal long-axis views were obtained through the long axis of the ventricle as defined by the maximal internal diameter at both the mitral valve level and the distal portion of the ventricle. Apical four-chamber views were obtained in a nonforeshortened plane with the maximal length of the LV long axis and maximal excursion of the mitral and tricuspid valves. Apical two-chamber views were obtained in a nonforeshortened plane with the same long axis as the apical four-chamber view and with no portion of the aorta visualized.

After image quality and gain settings were optimized for endocardial tracking by acoustic quantification (6), color kinesis was activated to color encode endocardial motion within a region of interest surrounding the LV cavity. For each imaging plane, three systolic and three diastolic color kinesis image sequences were acquired during end expiration and stored on optical disk (1 entire sequence and 2 single end-systolic or end-diastolic frames) for off-line analysis. Time settings of diastolic color encoding were adjusted when necessary (31, 44).

Analysis of color kinesis overlays. Digital images were analyzed at the University of Chicago using a previously described custom-designed software (31). Briefly, images were segmented based on segmentation schemes specific to each view. Segmentation schemes used for parasternal short axis as well as apical four- and two-chamber views (Fig. 1, *A*, *C*, and *D*) were previously described in detail (31). The parasternal long-axis images were partitioned based on four manually determined landmarks, including the base of the mitral and aortic valve leaflets (Fig. 1*B*, *points 1* and *4*) and the distal end of septal and posterior endocardium (Fig. 1*B*, *points 2* and *3*). *Points 1* and *3*, as well as *points 2* and *4,* were connected with two straight lines, the intercept of which was used as the origin of segmentation. This scheme excluded valve motion from the analysis similar to the apical views (31). Subsequently, each septal and posterior wall was divided into two equiangled segments (37). From both end-systolic and end-diastolic color overlays, pixels of each color were counted in each segment, and pixel counts were used to calculate different indexes of magnitude and timing of both

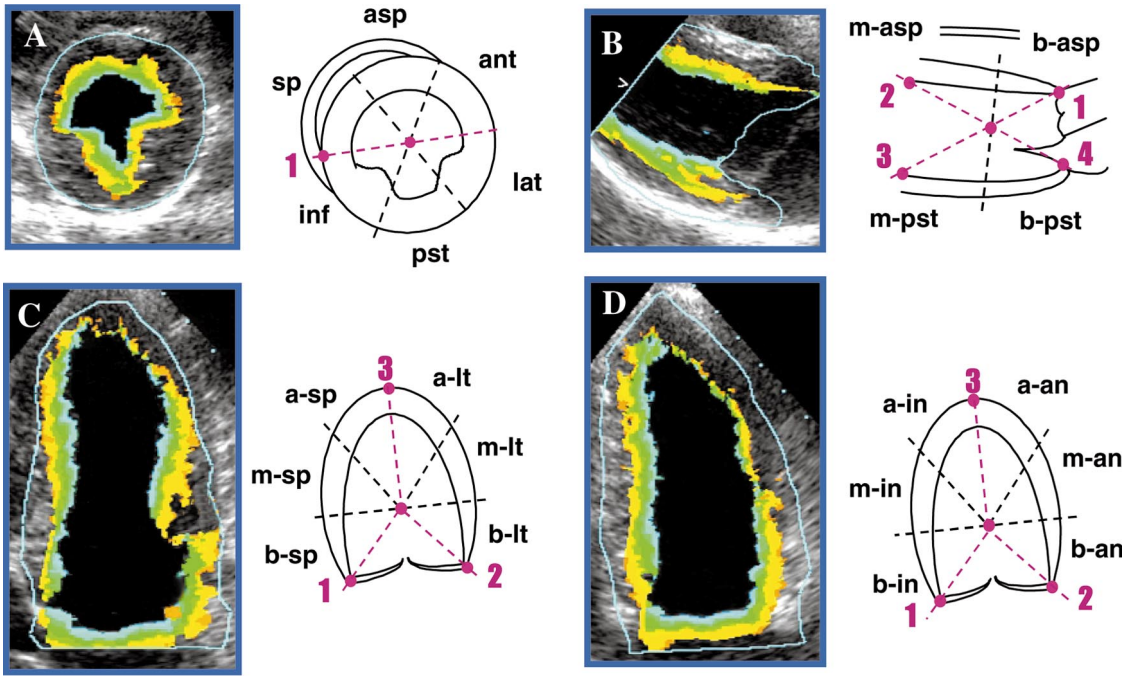

Fig. 1. Example of color kinesis images of the left ventricle obtained in a normal subject in 4 standard echocardiographic views with segmentation schemes used for analysis of endocardial motion: *A*: parasternal short axis view (SAX): ant, anterior; asp, anteroseptal; sp, septal; inf, inferior; pst, posterior; lat, lateral. *B*: parasternal long axis view (LAX): b-asp, basal anteroseptal; m-asp, midanteroseptal; m-pst, midposterior; b-pst, basal posterior. *C*: apical 4-chamber view (A4C): b-lt, basal lateral; m-lt, midlateral; a-lt, apical-lateral; a-sp, apical-septal; m-sp, midseptal; b-sp, basal-septal. *D*: apical 2-chamber view (A2C): b-an, basal-anterior; m-an, midanterior; a-an, apical-anterior; a-in, apical-inferior; m-in, midinferior; b-in, basal-inferior. Anatomic landmarks used for segmentation are shown (see METHODS for details).

Table 1. *Interinstitutional variability obtained by repeated acquisition and analysis of data from 6 normal subjects in 1 setting consecutively by 6 sonographers from different universities*

	SAX		A4C	
	Systole	Diastole	Systole	Diastole
Global indexes				
Fractional area change/filling fraction	9 ± 4	8 ± 3	10 ± 4	10 ± 5
Peak ejection/filling rate	14 ± 5	14 ± 5	11 ± 4	17 ± 7
Time to peak ejection/filling	6 ± 3	27 ± 14	5 ± 2	42 ± 14
Mean time of ejection/filling	7 ± 3	13 ± 6	5 ± 2	11 ± 5
Regional indexes				
Fractional area change/filling fraction	12 ± 3	10 ± 2	16 ± 6	16 ± 5
Mean time of ejection/filling	7 ± 3	12 ± 6	5 ± 2	11 ± 5

Values are SD in percent of the mean of repeated measurements (mean of 6 normal subjects ± SD). Thus 9 ± 4 for systolic fractional area change means that this index was measured in each subject 6 times by different operators, and the spread in the measured results was represented by an SD of the magnitude of 9% of their mean, when averaged for all 6 study subjects, with an SD of 4%. SAX, short-axis view; A4C, apical 4-chamber view.

global and regional LV endocardial motion. To account for interbeat variability, indexes obtained from three color kinesis images were averaged for each systole and diastole.

Quantitative analysis of global LV function. Global LV function was assessed for the parasternal short-axis view and both apical views, because the entire LV cavity could be visualized only in these views. This was done by using combined pixel counts from all endocardial segments to create time histograms of ejection and filling rate, which was expressed in units of LV end-diastolic area per second to allow intersubject comparisons. From these time histograms, peak ejection and filling rates, times-to-peak ejection and peak filling rates, and mean times of ejection and filling were calculated as described previously (31). In addition, the ratio of late to early ejection was calculated as percentage of LV cavity area ejected during the last 50% of LV ejection time divided by that ejected during the first 50%. Similarly, the ratio of late to early filling was calculated as percentage of LV cavity area added during the last 50% of LV filling time divided by that added during the first 50%.

Quantitative analysis of regional wall motion. Segmental pixel counts were used to evaluate regional endocardial wall motion during ventricular ejection and filling in terms of incremental fractional area change and filling fraction, which was expressed in percentage of regional end-systolic area and displayed as stacked histograms (27, 31). The temporal aspects of regional wall motion were expressed by mean time of ejection and mean time of filling calculated for each segment (31, 46). In addition, normalized ejection and filling time curves were generated for each segment to facilitate the assessment of temporal patterns of endocardial motion without the confounding effects of magnitude of motion in each segment (19, 31, 44). From these curves, an index of LV systolic and an index of LV diastolic asynchrony were calculated as the SD of the mean percentage of regional ejection and filling at 50% ejection and filling time, respectively, in all 22 segments in four views.

Reproducibility. The reproducibility of color kinesis indexes of LV function was studied by the imaging of six normal subjects (age 23 ± 5 yr) by sonographers from six different institutions, consecutively, in one setting, using the same imaging systems. Each sonographer acquired three end-systolic and three end-diastolic images in the parasternal short-axis and apical four-chamber views. Images were analyzed, and indexes of global and regional endocardial motion were calculated as described above by averaging the results of the three repeated measurements. Interinstitutional variability in each index was calculated as SD in percentage of the mean of the values obtained by all participants.

Statistical analysis. All calculated indexes were expressed as means ± SD of the entire group of subjects. The variability of each index was calculated as the SD in percentage of the mean. To test the effects of gender on each index, mean values and SDs were calculated for male versus female subjects separately. Similarly, to study the effects of age, mean and SD of each index were calculated for each decade of age separately. Analysis of variance was used to test significance of differences between genders and age groups, which was defined at $P < 0.05$.

RESULTS

The results of the interinstitutional variability protocol are summarized in Table 1. Global fractional area change was reproducible within 10% of the mean for both the short-axis and apical four-chamber views in systole and diastole. Peak ejection and filling rates were reproducible between 11 and 17% of the mean. Time-to-peak ejection and mean time of ejection, as well as mean time of filling, were highly reproducible. In contrast, time-to-peak filling showed much higher variability (Table 1). Regional fractional area change and filling fraction both showed slightly higher variability than their global counterparts. However, regional mean time of ejection and filling followed closely their global counterparts in their levels of reproducibility (Table 1). There were no differences between segments in each view for any of the indexes studied.

To establish normal values for color kinesis indexes of global and regional LV function, images were acquired in 194 normal subjects (Table 2). Data obtained in 7 of 194 subjects were not included for technical reasons, such as corrupted data files ($n = 5$) and incorrect timing of diastolic color-encoding ($n = 2$). Figure 2 presents the summary of indexes of global LV function averaged for 187 subjects. The temporal patterns of rate of area change during LV ejection and filling were similar in the different views (Fig. 2, *top*),

Table 2. *Age and gender distribution of the study population by groups*

Age Group	*n*	Age, yr
0–9 yr	29(14m/15f)	5.4 ± 2.9
10–19 yr	20(10m/10f)	14.5 ± 3.3
20–29 yr	30(15m/15f)	24.3 ± 2.5
30–39 yr	29(16m/13f)	33.3 ± 2.5
40–49 yr	26(14m/12f)	43.3 ± 2.9
50–59 yr	21(9m/12f)	52.5 ± 2.7
60–69 yr	21(9m/12f)	64.2 ± 3.0
70–79 yr	18(8m/10f)	74.4 ± 5.8

m, Male; f, female.

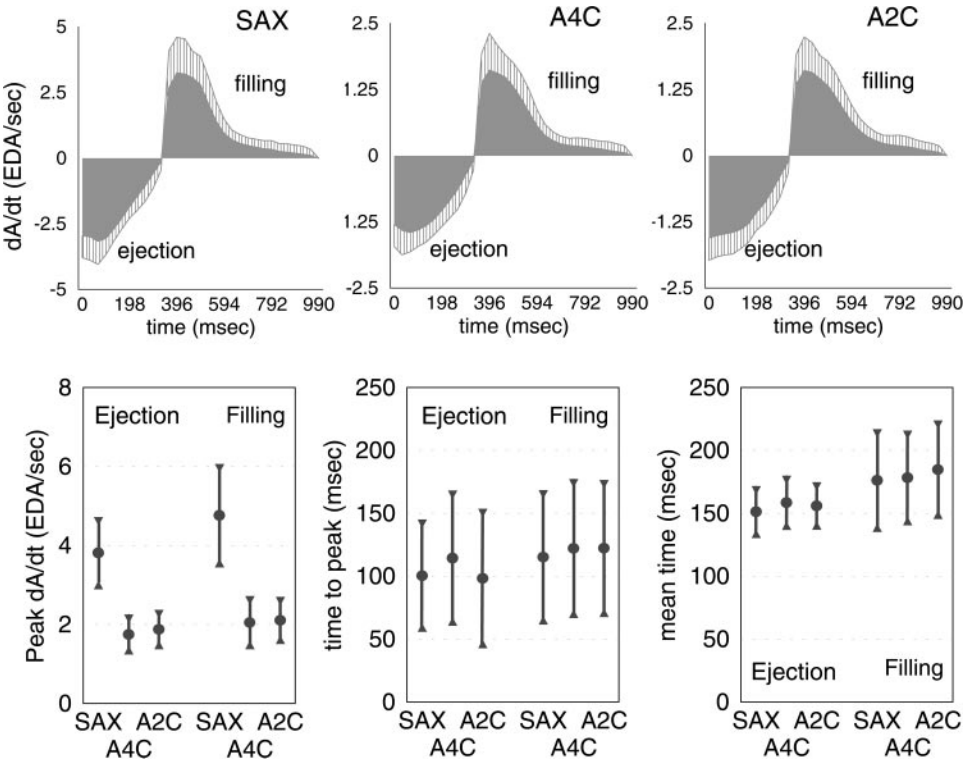

Fig. 2. Indexes of global left ventricular (LV) function averaged for 187 normal subjects (95 males, 99 females, age 2 mo to 79 yr). Rate of LV ejection and filling over time (*top*, dashed band represents 1 SD) in end-diastolic areas per second (EDA/sec) was used to obtain peak ejection and filling rates (*bottom left*), time-to-peak ejection and filling rate (*bottom middle*), and mean time of ejection and filling (*bottom right*). Error bars represent 1 SD around the mean. Variability in each index is shown as SD in percentage of the mean.

apart from magnitude differences: both ejection and filling rates were twice as high in the short-axis view as in the apical four- and two-chamber views, which were almost identical. Peak ejection and filling rates derived from these data were consistent with the above differences between views and showed intersubject variability of 22 and 25% of the mean, correspondingly. Time-to-peak ejection and time-to-peak filling were similar in all views and showed levels of variability over 40% of the mean. In contrast, mean time of ejection varied

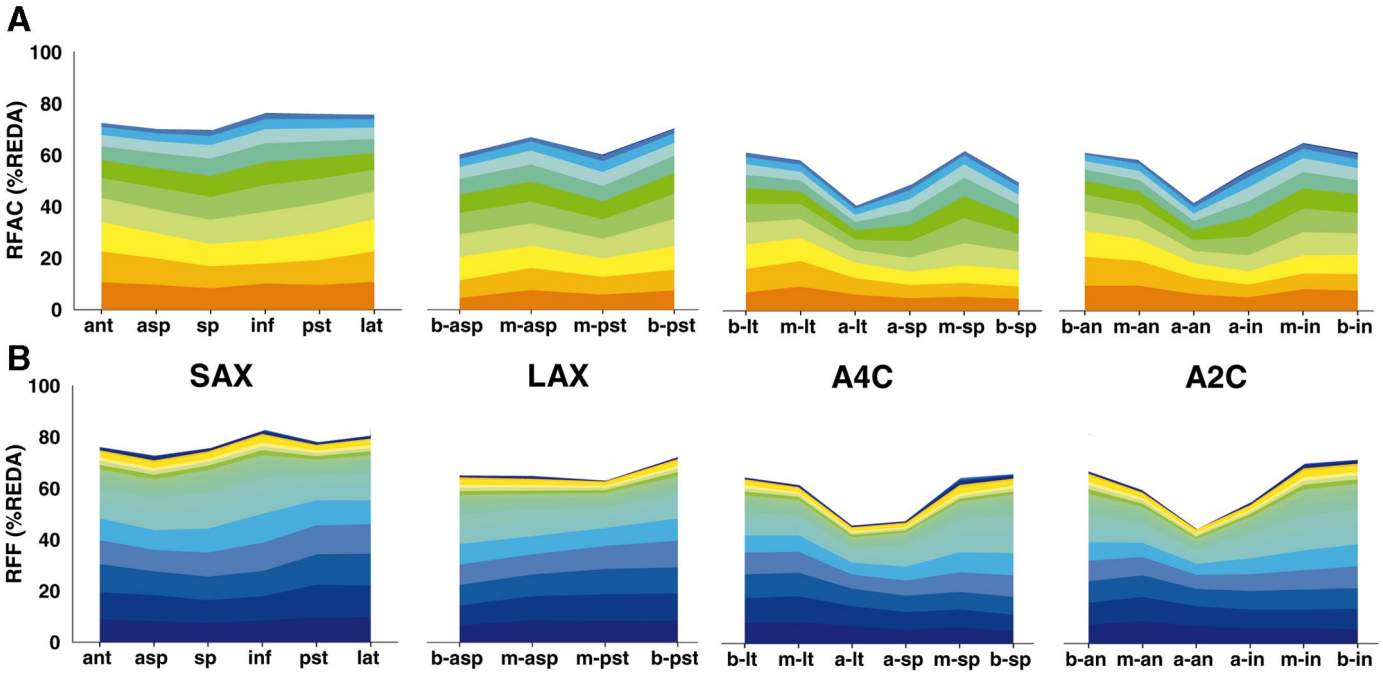

Fig. 3. Stacked color histograms of regional systolic fractional area change (RFAC, *A*) and regional diastolic filling fraction (RFF, *B*) obtained in 187 normal subjects. Each layer of these histograms represents incremental fractional area change that occurred during a 33-ms period of time, with earliest motion being shown on the bottom layer and latest motion at the top layer of the histograms. REDA, regional end-diastolic area; view and segment notations are same as in Figs. 1 and 2.

Table 3. *Summary of indexes of regional LV endocardial motion obtained in all study subjects and in adult subjects only in 4 standard echocardiographic views: RFAC, RFF, MTE, and MTF*

	n = 187, Age 2 mo to 79 yr				n = 141, Age 20–79 yr			
	RFAC, %REDA	RFF, %REDA	MTE, ms	MTF, ms	RFAC, %REDA	RFF, %REDA	MTE, ms	MTF, ms
SAX								
ant	73 ± 12	76 ± 11	143 ± 19	178 ± 42	74 ± 11	77 ± 10	146 ± 17	190 ± 36
asp	70 ± 12	73 ± 12	149 ± 23	186 ± 47	72 ± 10	74 ± 11	153 ± 21	198 ± 43
sp	70 ± 12	76 ± 12	159 ± 23	189 ± 46	72 ± 11	76 ± 11	163 ± 19	203 ± 40
inf	76 ± 11	83 ± 10	160 ± 25	187 ± 46	77 ± 10	83 ± 9	166 ± 21	200 ± 39
pst	76 ± 11	78 ± 10	154 ± 23	162 ± 35	75 ± 10	78 ± 9	158 ± 20	171 ± 30
lat	76 ± 12	81 ± 10	144 ± 20	167 ± 40	77 ± 10	81 ± 10	147 ± 18	177 ± 35
A4C								
b-lt	62 ± 12	65 ± 13	151 ± 24	175 ± 36	63 ± 12	67 ± 12	154 ± 24	185 ± 31
m-lt	59 ± 12	61 ± 14	141 ± 22	164 ± 35	59 ± 12	63 ± 13	145 ± 21	173 ± 30
a-lt	42 ± 12	46 ± 13	147 ± 20	164 ± 29	42 ± 12	47 ± 13	153 ± 17	171 ± 25
a-sp	49 ± 13	48 ± 13	171 ± 23	174 ± 37	51 ± 13	50 ± 12	176 ± 18	185 ± 31
m-sp	62 ± 12	63 ± 13	170 ± 24	195 ± 55	65 ± 11	67 ± 11	173 ± 21	212 ± 48
b-sp	50 ± 12	65 ± 12	167 ± 24	198 ± 46	51 ± 12	67 ± 11	173 ± 20	215 ± 34
A2C								
b-an	62 ± 12	67 ± 14	137 ± 19	191 ± 43	62 ± 12	69 ± 13	140 ± 17	204 ± 36
m-an	59 ± 13	59 ± 14	140 ± 18	170 ± 34	60 ± 12	62 ± 13	144 ± 16	179 ± 31
a-an	42 ± 11	45 ± 13	149 ± 17	162 ± 24	43 ± 11	47 ± 12	154 ± 15	168 ± 20
a-in	55 ± 18	54 ± 15	175 ± 22	178 ± 39	57 ± 19	57 ± 14	179 ± 20	189 ± 32
m-in	66 ± 18	69 ± 15	162 ± 22	204 ± 54	68 ± 19	72 ± 14	165 ± 21	220 ± 46
b-in	62 ± 14	71 ± 14	160 ± 23	200 ± 52	63 ± 14	73 ± 13	165 ± 21	215 ± 46
LAX								
b-asp	60 ± 13	65 ± 13	163 ± 22	192 ± 48	59 ± 14	65 ± 14	167 ± 18	208 ± 39
m-asp	67 ± 14	64 ± 15	160 ± 24	174 ± 39	67 ± 14	66 ± 15	162 ± 23	185 ± 33
m-pst	60 ± 17	63 ± 19	169 ± 28	158 ± 37	60 ± 17	64 ± 19	172 ± 26	168 ± 34
b-pst	71 ± 13	72 ± 14	159 ± 24	173 ± 39	69 ± 13	73 ± 14	162 ± 22	182 ± 36
Variability, %mean	22	21	14	23	21	19	12	18

Data represent means ± SD. Variability in each index (*bottom*) is expressed as SD in percentage of the mean. *Left,* summary of indexes of regional left ventricular (LV) endocardial motion obtained in all study subjects; *right,* summary of adult subjects only. RFAC, systolic fractional area change; RFF, diastolic filling fraction; MTE, mean time of injection; MTF, mean time of filling; REDA, regional end-diastolic area. View and segment notations are same as in Figs 1–3.

within only 11% of the mean and mean time of filling varied within 20% of the mean.

Figure 3 presents stacked color histograms of incremental regional fractional area change and filling fraction averaged in 187 subjects. The histograms showed the differences between views and segments for both LV ejection and filling. Fractional area changes were the highest in the short-axis view. Both parasternal views showed uniform motion patterns with minimal variations between segments. Both apical views showed reduced wall motion in the apical segments, in particular the apical-lateral segment in the apical four-chamber view and the apical-anterior segment in the apical two-chamber view. In addition, although the overall patterns of regional wall motion in different views were similar between systole and diastole, diastolic filling fractions were consistently slightly higher than systolic fractional area changes in most segments (mean difference of 4.1%).

Table 3, *left*, summarizes the indexes of regional wall motion in all study subjects. Regional fractional area changes and filling fractions for all segments showed variability of just above 20% of the mean for both systole and diastole. Mean times of ejection and filling showed minor differences between views and between segments within each view and with respective variability levels of 14 and 23% of the mean.

Figure 4 shows an example of the normal limits of normalized regional ejection and filling time curve for one segment. Such curves were obtained for each segment in all four views. Close examination of these curves revealed intersegmental differences in the temporal patterns of motion of the different segments. Most segments showed narrow tolerance lim-

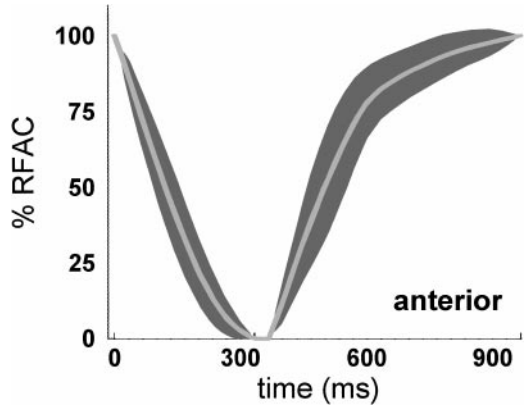

Fig. 4. Normalized regional LV ejection and filling time-curves were obtained for each segment in each view by averaging data from 187 normal subjects. The curve shown represents the anterior wall in the parasternal short-axis view. Shaded bands around the curve represent SDs around the mean.

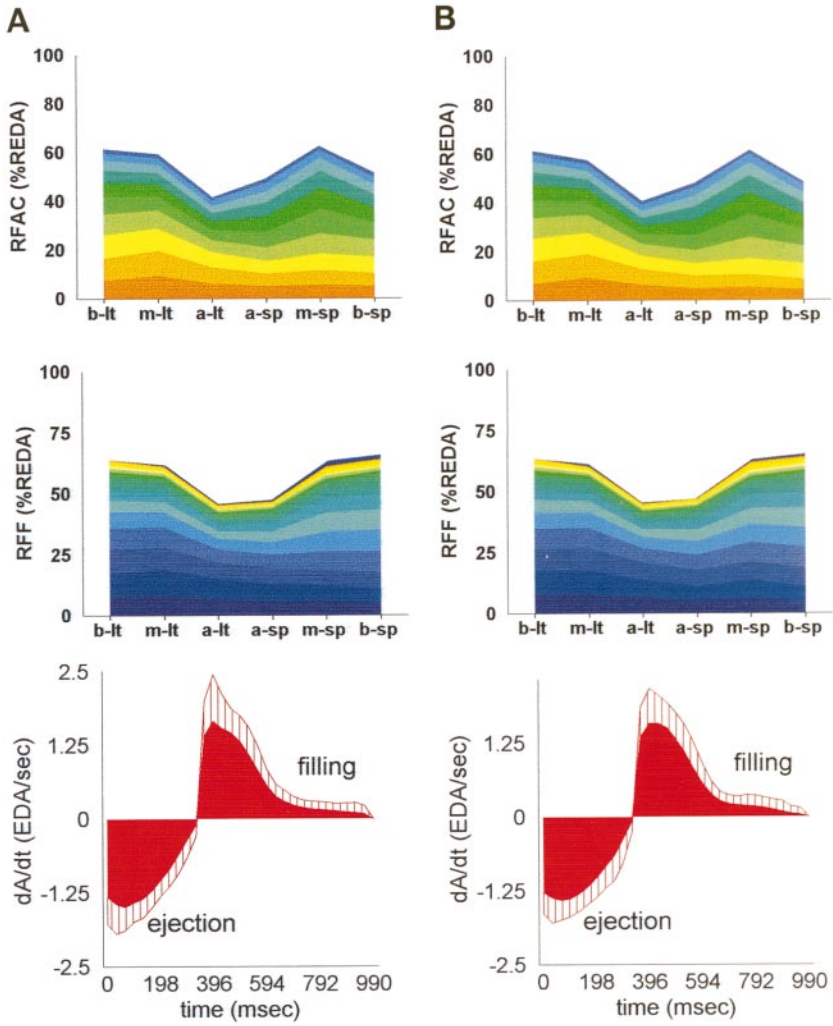

Fig. 5. Stacked color histograms of RFAC (*top*) and RFF (*middle*), and rate of LV ejection and filling over time (*bottom*) obtained in 92 male normal subjects (*A*) and 95 female normal subjects (*B*) in the apical 4-chamber view.

its reflected by the width of the SD band around the mean.

Figure 5 presents systolic and diastolic fractional area change histograms and time histograms of rate of area change obtained in two different gender groups: 92 males and 95 females. These data were virtually identical, and no gender-related differences were found in any indexes of either systolic or diastolic LV performance on a global as well as regional basis.

Figures 6 and 7 show the effects of age on global and regional diastolic performance, as assessed by analysis of color kinesis images. Regional filling fraction histograms (Fig. 6, *top*) demonstrate how the relative contribution of early filling, reflected by the lower blue layers, gradually decreased, whereas the contribution of the late filling, reflected by the upper color layers, increased with age. These changes were quantitatively confirmed by corresponding age-related variations in mean filling time (Fig. 6, *middle*). Similarly, time histograms of filling rate (Fig. 6, *bottom*) showed gradual age-related reduction in peak filling rate with a concomitant shift of the peak toward later filling and increasing dependency on late filling. Figure 7 summarizes the effects of age on different indexes of global LV diastolic endocardial motion. Although LV filling fraction remained unchanged, peak filling rate gradually decreased (Fig. 7, *top*), whereas mean filling time and late-to-early filling ratio increased with age (Fig. 7, *middle* and *bottom*). The differences between the different age groups were significant for each of these variables. Table 4 presents a subset of these data, where gender-related differences were revealed in the sixth decade of life. Both mean time of filling and late-to-early filling ratio showed a significant increase in female subjects when compared with previous age decades as well as with male subjects of the same age group.

Figures 8 and 9 show in a similar format the effects of age on systolic endocardial motion. Regional ejection fraction histograms (Fig. 8, *top*) demonstrated the gradual increase in the relative contribution of late ejection, reflected by the increasing thickness of the blue layers in the histograms. Mean ejection time gradually went up with age (Fig. 8, *middle*). Time histograms of ejection rate (Fig. 8, *bottom*) showed the gradual temporal shift toward augmented late LV ejection with age. Figure 9 summarizes the effects of age on different indexes of global LV systolic endocardial

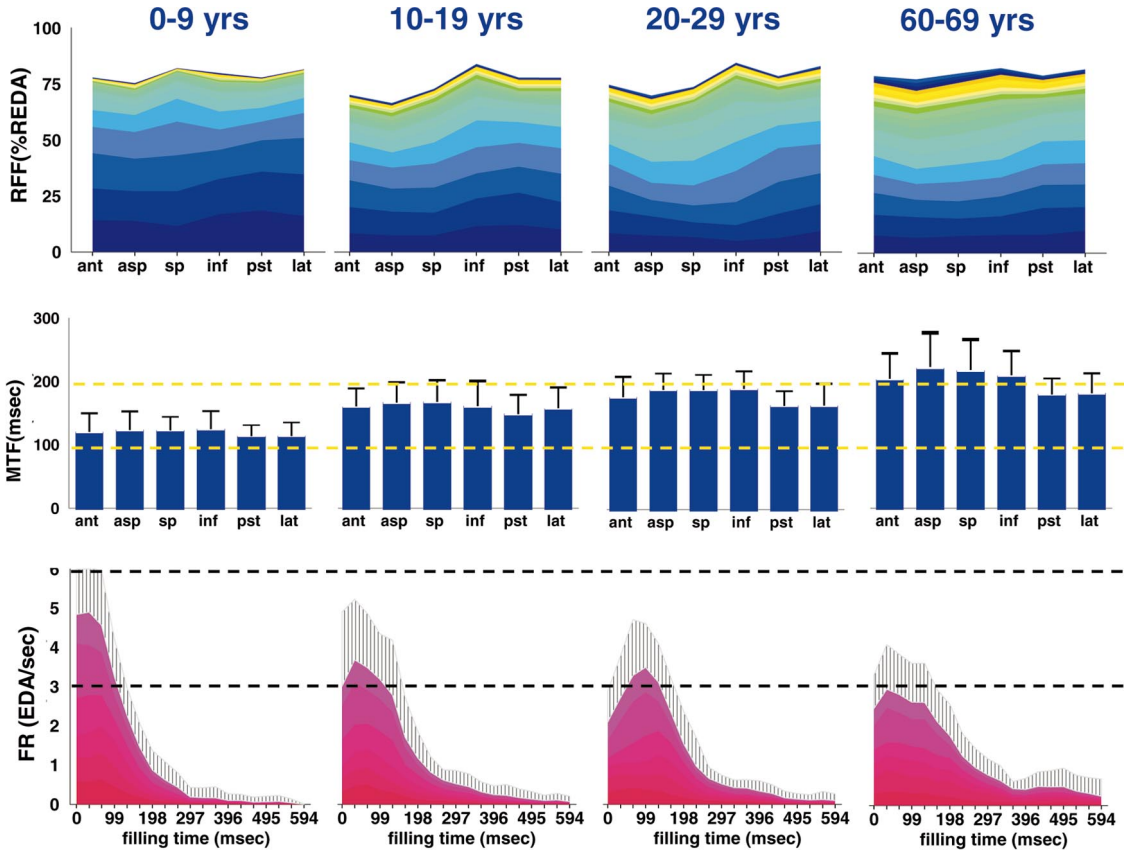

Fig. 6. Effects of age on diastolic endocardial motion: RFF (*top*), mean time of filling (MTF: *middle*), and filling rate (FR) over time (*bottom*). Data shown were obtained in the short-axis view from 4 different age groups (from *left* to *right*) of normal subjects of both genders (data from 30–39, 40–49, 50–59, and 70–79 are not shown). Dashed horizontal grid lines are shown to facilitate the visualization of age related changes. Error bars and dashed bands represent SDs.

motion. Despite invariable fractional area change, peak ejection rate showed a trend of decrease in the first decades (Fig. 9, *top*), with concomitant increase in both mean time of ejection and late-to-early ejection ratio (Fig. 9, *middle* and *bottom*). The differences between the age groups were also significant for each of these indexes.

Figure 10 shows ejection and filling curves obtained in the same endocardial segment averaged over all subjects in the different age groups. The age-related differences in the diastolic portion of the curves demonstrated the decreasing rate of rapid LV filling with increasing dependence on atrial contraction. Although less pronounced, the systolic portion of the curves also demonstrated an age-related decrease in the rate of LV ejection.

Index of diastolic asynchrony calculated at 50% filling time showed clear age dependency (Fig. 11). With the exception of the first decade, diastolic asynchrony progressively increased with age, although this increase reached statistical significance only in the oldest two groups. In contrast, systolic asynchrony showed no age-related trend.

In view of the above age-related differences, normal values of regional endocardial motion were recalculated by averaging each index for the adult subjects only (n = 141, age 20 and up; Table 3, *right*). Although regional fractional area changes and filling fractions were not affected significantly by excluding the children, regional mean times of both LV ejection and filling went up ~10%. Also, SDs decreased in all segments, in particular for mean time of filling, which showed average decrease from 23 to 18% of the mean.

DISCUSSION

Various approaches have been explored to circumvent the subjective nature of the interpretation of LV wall motion (12), which is at times referred to as the "bread and butter" of echocardiography (16, 17, 21, 33, 34). However, most of these techniques are based on time-consuming tracing of endocardial borders and therefore remain subjective and impractical for routine clinical use. Other computerized techniques either required extensive off-line processing (4, 38) or were limited to specific imaging planes (15, 40). Recently, new techniques, such as color-enhanced motion analysis and tissue Doppler imaging, have been shown to potentially objectively assess regional LV function (5, 42).

The development of automated boundary detection based on acoustic quantification allowed continuous

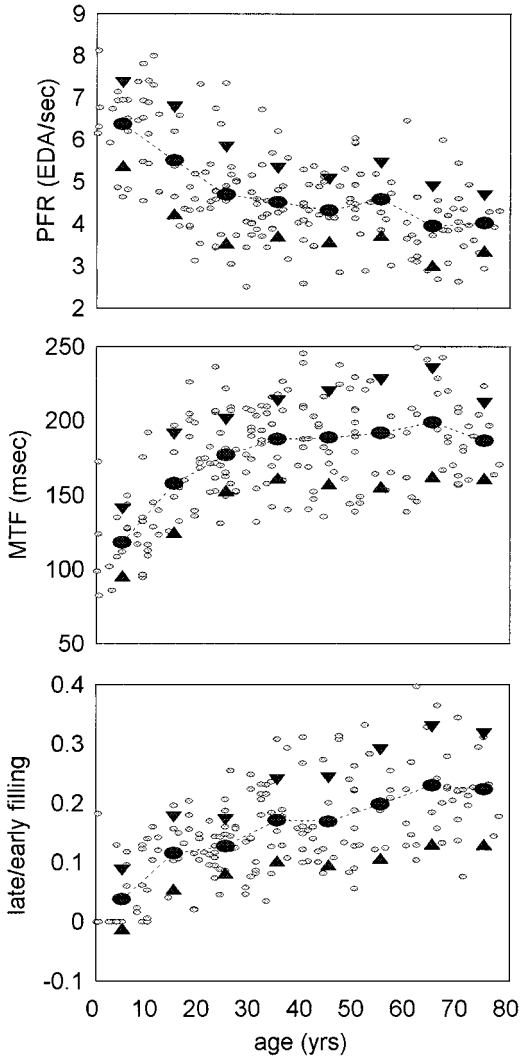

Fig. 7. Summary of indexes of LV diastolic endocardial motion (short-axis view) plotted against age: PFR, peak filling rate; MTF; and late-to-early filling ratio. ●, Mean values of each age group; ▼ and ▲, 1 SD above and below the mean, respectively; ○, individual subject data.

real-time measurements of LV cross-sectional area, obviating the need for manual tracing of the endocardial boundary to quantitatively assess global ventricular function (35). Recently, the ability of a related technique, color kinesis, has been evaluated as an aid for the evaluation of regional wall motion (28, 39, 43, 46). We have previously described a method of segmental analysis of color kinesis images, which provides quantitative indexes of magnitude and timing of regional LV endocardial motion (31). This technique has been used to objectively identify wall motion abnormalities in patients with coronary artery disease at rest (27) and under conditions of dobutamine stress testing (25) and allowed us to characterize regional filling asynchrony in patients with diastolic dysfunction due to LV hypertrophy (44) and dilated cardiomyopathy (19).

Segmental analysis of color kinesis images provides a unique noninvasive tool for objective assessment of regional LV systolic and diastolic performance without radioisotopes. By directly quantifying the magnitude and timing of LV endocardial motion, it is potentially less affected by factors that are known to confound the traditional indirect assessment of LV function. However, for this technique to provide the basis for reliable diagnosis of regional systolic and diastolic dysfunction with high levels of confidence, normal values need to be established for different indexes derived from color kinesis images. Accordingly, the goal of this study was to establish normal values for magnitude and timing of wall motion by acquiring and analyzing color kinesis images in a large group of normal subjects over a wide range of ages.

With the results of this study, this technique becomes the only echocardiographic technique to have established normal values of regional LV systolic and diastolic function. These values were similar to those established by other imaging modalities, in particular radionuclide ventriculography (8). Importantly, most indexes of magnitude and timing of LV endocardial motion during LV ejection and filling showed levels of reproducibility similar to those described for parameters routinely used in clinical cardiology (8), even when obtained from data acquired by sonographers from different laboratories. The low level of variability in these indexes established the basis for their use to characterize endocardial motion in a large sample of the normal population.

Interpretation of results. Because our sample of the normal population was near 200 subjects, we may assume that 75% of normal subjects should fit into a range defined by 1 SD around the mean of our sample and 95% of normal subjects should fit into a 2 SD range with 95% confidence (18). As data in Figs. 7 and 9 suggest, a large proportion of subjects that do not fit into the adult normal ranges are children in the first decade of life. Therefore, SDs calculated for the adults (Table 3) should provide even tighter confidence intervals than those obtained for the entire group of normal subjects.

The histograms of regional fractional area change and filling fraction (Fig. 3) reflected patterns of uniform endocardial motion, with the exception of segments affected by "ultrasound drop-out." This general technical limitation of ultrasound imaging is well known and is explained by the reduced echogenicity in

Table 4. *Temporal indexes of LV filling separated according to age and gender to demonstrate pre- and postmenopausal changes*

	MTF		Late/Early Filling	
Age Group	Male	Female	Male	Female
30–39 yr	194 ± 21	180 ± 29	0.18 ± 0.06	0.16 ± 0.08
40–49 yr	193 ± 31	184 ± 30	0.18 ± 0.07	0.15 ± 0.08
50–59 yr	198 ± 46	188 ± 25	0.24 ± 0.10	0.17 ± 0.07
60–69 yr	191 ± 33	205 ± 37*†	0.18 ± 0.04	0.26 ± 0.11*†

Values are means ± SD. *$P < 0.05$ vs. other age groups, †$P < 0.05$ vs. male subjects of the same age.

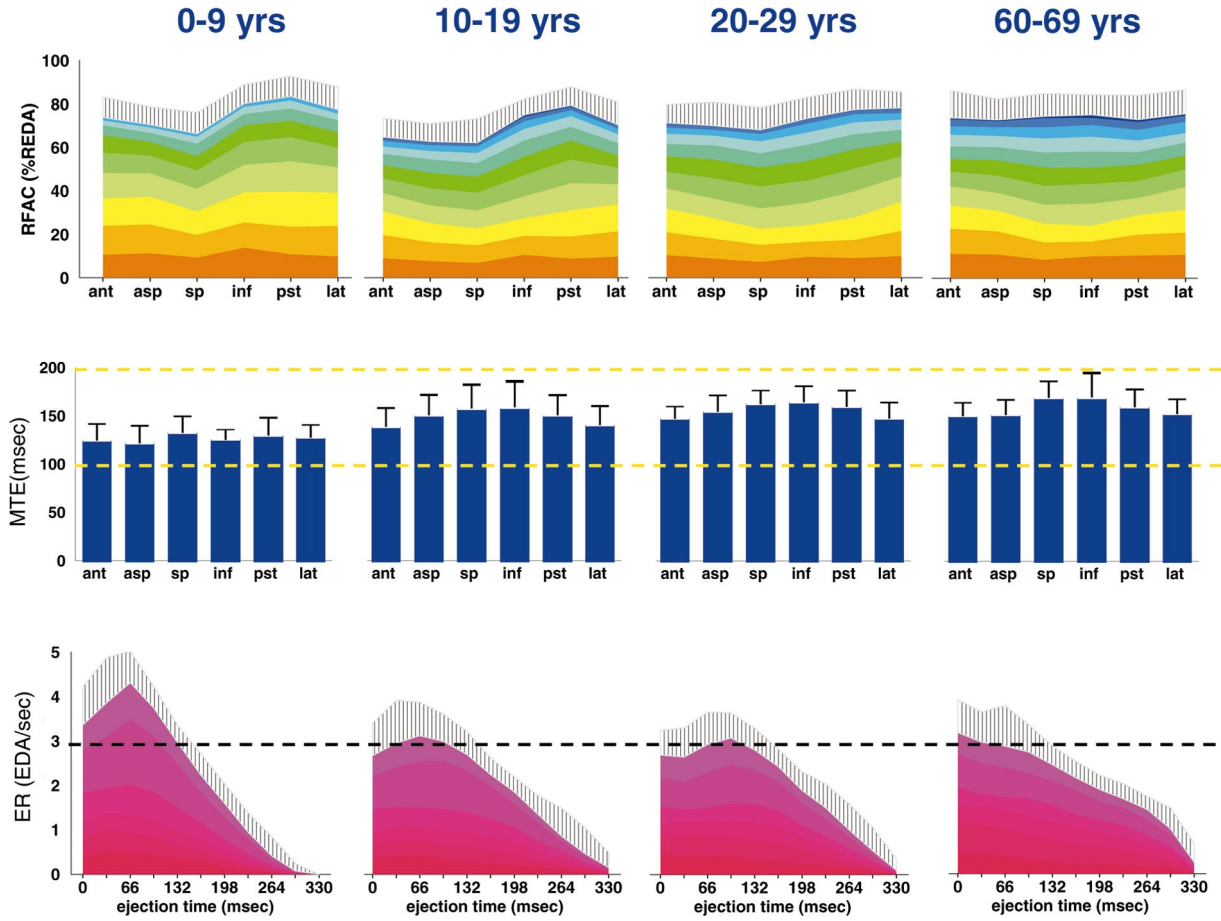

Fig. 8. Effects of age on systolic endocardial motion: RFAC (*top*), MTE (*middle*), and ejection rate (ER) over time (*bottom*). Data are shown in the same format as in Fig. 6.

segments where muscle fibers are parallel to the ultrasound beam. We also found that rate of area changes observed in the short-axis view was significantly higher than those measured in the apical views. This finding is consistent with the known differences in fractional area changes between views, which reflect the differences between motion patterns of the three-dimensional ventricle viewed in different cross-sectional planes (4, 12, 16, 17, 21, 33, 34, 37, 38). These differences are understandable, because different echocardiographic views depict different regions of three-dimensional endocardial surface throughout its complex, nonuniform motion. The differences between systolic fractional area changes and diastolic filling fractions may be explained as follows. Because pixel transitions between blood and tissue in consecutive video frames may be a result of ultrasound speckle noise, as well as cardiac translation, the number of pixels, which are color coded in diastole, may be larger than in systole, because LV filling lasts longer than ejection.

Mean times of ejection and filling showed variability <20% of the mean in the adult subjects (Tables 1 and 3), which defines narrow confidence intervals for these temporal indexes of LV function. In contrast, time-to-peak filling rate showed two to four times higher variability than mean time of filling. This difference can be explained by the fact that the former depends on accurate identification of the onset of diastole and the peak of filling rate, which are both limited by the frame rate of color-encoded imaging. In this regard, mean time is superior to time to peak and should provide more reliable information on the temporal aspects of LV wall motion. We believe that this superiority will outweigh the fact that time-to-peak indexes have been previously used to assess LV function, whereas mean times are new and less intuitive. Also, calculating these indexes is less demanding than accurate identification of peaks in noisy data such as LV area changes over time.

The normal variability in the magnitude of area changes was similar in systole and diastole (Table 3). However, based on data in Figs. 7 and 9, mean time of filling was affected by age almost three times as much as mean time of ejection, which explains the relatively high variability in the former parameter in a group of normal subjects over a wide range of ages (Table 3, *left*). This variability was reduced by eliminating children's data from the normal values established for the adults (Table 3, *right*).

Regional ejection and filling curves presented in Fig. 4 provide detailed information about temporal patterns of regional LV endocardial motion, which is the

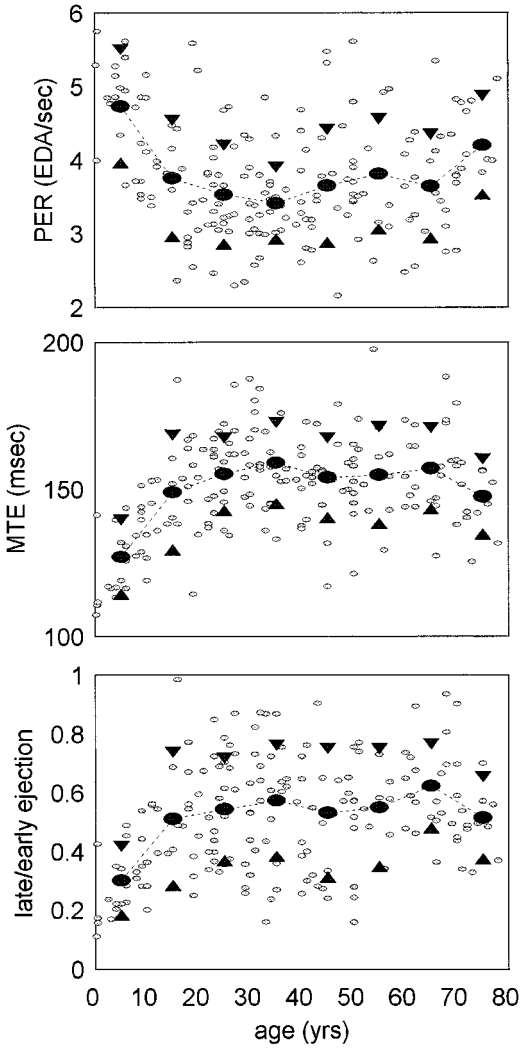

Fig. 9. Summary of indexes of LV diastolic endocardial motion (short-axis view) plotted against age: PER, MTE, and late-to-early ejection ratio. Data are shown in the same format as in Fig. 7.

advantage of these curves over other temporal indexes. Of course, mean value of a distribution does not tell much about its width or shape, which may be valuable, in particular for functions that differ from normal distribution as much as the multiphasic LV filling. On the other hand, the advantage of the mean times of ejection and filling is the simplicity of a single value compared with the complexity of a curve.

LV diastolic function is known to be age dependent (2, 9, 24, 36). Age-related decrease in the rate of rapid LV filling and the increasing dependency of LV filling on left atrial contraction have been recognized by previous investigators who used spectral-Doppler transmitral inflow profiles to study different pathologies involving diastolic dysfunction (1, 10, 30). In this study, we successfully tested the ability of segmental analysis of color kinesis images to quantitatively demonstrate this trend (Figs. 6, 7, and 10) consistently with the previous findings. Unlike Doppler measurements, however, this new technique was found capable of demonstrating the known age dependency of LV filling

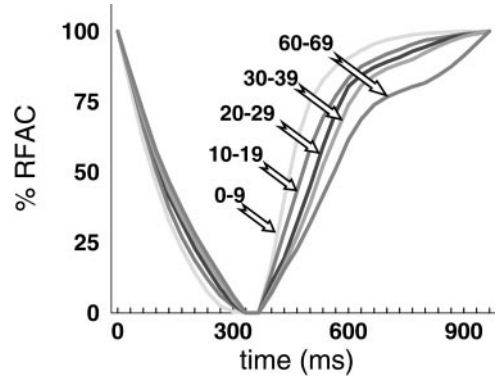

Fig. 10. Example of regional LV ejection and filling curves obtained from 1 segment by averaging data in different age groups: 0–9, 10–19, 20–29, 30–39, and 60–69 yr. The differences between curves demonstrate the effects of age on both regional LV ejection and filling (see METHODS for details).

properties on a regional basis (Fig. 10). In addition, our analyses confirmed an increase in normal diastolic heterogeneity with age (Fig. 11) previously reported by Bonow and coworkers (8) who used radionuclide ventriculography to study regional LV filling. This finding may reflect uneven effects of age on different parts of the myocardium, such as regional variations in loading conditions, myocardial activation/inactivation, collagen content, and others. Clinically, the ability to assess LV function on a regional basis (14) will undoubtedly prove important for the diagnosis of pathologic states that do not necessarily or immediately affect myocardial function globally, such as coronary artery disease (49).

Our results did not reveal any gender dependency in either LV systolic or diastolic performance when all male subjects were compared with all females regardless of age. However, closer examination of simultaneous age- and gender-related effects revealed a significant delay in global LV filling with increased dependency on late filling in women over 60 years of age (Table 4), in agreement with recent observations of other investigators (22, 47). Moreover, close examination of data in Figs. 5, 6, and 8 provided additional

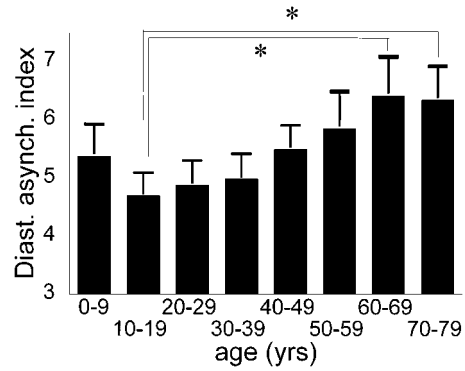

Fig. 11. Index of diastolic asynchrony (Diast. asynch.) represented by the spread between segments in percentage of LV filling at 50% filling time. Data represents mean and SE for each age group; *$P <$ 0.05.

support to the robustness of our methodology, because the patterns of regional variations shown in these figures are almost identical, although obtained in completely nonoverlapping groups of subjects of different genders and ages.

In contrast to the age dependency of LV diastolic function in normal subjects, the effects of age on temporal patterns of LV systolic function are less well known. In this study, we found that the temporal indexes of normal LV systolic endocardial motion are also affected by age (Figs. 8–10) similarly to indexes of diastolic function, although to a lesser extent (Figs. 9 and 10). Specifically, we found that with age, in particular in the first decades of life, LV ejection depends more on late ventricular contraction (Figs. 8–10). This interesting finding is consistent with previous results obtained using load-independent analysis of rate-corrected velocity of circumferential fiber shortening and wall stress from echocardiographic images (11, 13, 23), which were explained by an age-related decrease in contractility and increase in afterload (11). This finding should not be surprising, as the effects of age may mimic mild contractile dysfunction, similar to the relationship between filling abnormalities and age-related changes in normal diastolic function.

Our analyses also revealed systolic asynchrony (Fig. 11), which may reflect normal heterogeneity in LV contractile properties as well as regional differences due to normal activation sequences. The ability to noninvasively assess LV systolic asynchrony may also prove advantageous for early diagnosis of myocardial ischemia (3, 7, 26, 48). Interestingly, unlike the heterogeneity in LV filling, we found that the systolic asynchrony observed in normal subjects was not age dependent, in agreement with previous findings (8). Accordingly, increased systolic asynchrony may be related to LV contraction abnormalities without accounting for patients' age.

Limitations. Our study included normal subjects in a very wide age range. Ruling out coronary artery disease was one of the important enrollment criteria, in particular in the older age groups. Although echocardiographic confirmation of normal systolic function with no evidence of wall motion abnormalities could not conclusively rule out coronary artery disease, we excluded subjects with regional left ventricular dysfunction as an attempt to reach this goal.

We previously discussed in detail the limitations of color kinesis and those of segmental analysis that was developed to quantify endocardial motion from color-encoded images (19, 27, 44) These limitations should be carefully considered by users of these techniques. The main limitation of this technique is most likely the ability of acoustic quantification technology to accurately track the endocardial motion throughout the cardiac cycle, which is directly related to image quality. Another important limitation of this technique is that it uses endocardial motion alone, without simultaneously assessing myocardial thickening and is, therefore, under certain conditions prone to translation artifacts. This can explain the differences between our data and the known increased thickening from base to apex. However, these limitations are outweighed by the fact that the combination of these techniques offers objective quantitative information directly related to magnitude and timing of regional endocardial motion, whereas we still routinely rely on our senses and our subjective experience to qualitatively assess these physiological variables in clinical practice.

Another potential limitation to the accuracy of our findings is the lack of direct validation of these findings with other established independent techniques. However, technologically, color kinesis is an offspring of automated endocardial border detection based on acoustic quantification, which has been extensively validated in multiple studies against true ventricular volumes in animals (20, 32), as well as magnetic resonance imaging (41) and ultrafast computed tomography (29) in patients. Color kinesis uses a different display of the same acoustic information as automated border detection, which promises similar levels of accuracy.

Yet another important limitation of color kinesis is its low temporal resolution determined by the frame rate of the imaging system. In particular, this technical limitation might have adversely affected the variability of time-to-peak filling rate in this study. Newer digital imaging systems, however, allow color encoding of endocardial motion at higher frame rates, which promise to circumvent this limitation in the future.

In this study, we found that age-related differences in both systolic and diastolic LV function are most pronounced in the first decades of life. Therefore, it would be beneficial to have more young normal subjects enrolled and to subdivide the young group, because averaging data from newborns with those of 9 year olds may have obliterated some age-related effects. However, we could not justify continuing efforts associated with further expanding data acquisition in children.

Also, measurements of regional systolic emptying and diastolic filling are derived from segmental area changes. Because the geometry of the LV cavity may be affected by age (e.g., a decrease in long-axis dimension and changes in the shape of the basal anterior septum), some of the age-dependent differences in regional function described here could be related to these geometric changes. However, normal values are an absolute requirement for a new technique to become useful, regardless of all possible factors that play a role in determining these values.

In summary, this multicenter study was designed to establish normal values for indexes of magnitude and timing of LV endocardial motion derived from color kinesis images. This goal was achieved by acquiring and analyzing data in a large group of normal subjects. The normal values established in this study provide the basis for an objective assessment of LV systolic and diastolic function. It should be particularly beneficial for the diagnosis of regional systolic and diastolic dysfunction, which is currently highly subjective and experience dependent. This new diagnostic technique

may provide additional information to those currently used in clinical practice and may thus improve the diagnostic value of echocardiography. In addition, our results demonstrated the unique ability of segmental analysis of color kinesis images to quantify age-related changes in global as well as regional LV systolic and diastolic function. These interesting findings include an age-related increase in LV diastolic asynchrony and augmented contribution of late LV ejection that occurs with age.

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