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The Characteristic Sequence for the Onset of Contraction in the Normal Human Left Ventricle

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SUMMARY **The sequence for the onset of segmental contraction of the left ventricle was studied in 25 normal patients by analyzing sequential frames obtained at 16.7-msec intervals of right anterior oblique (RAO) ventriculograms by two independent methods. In the first method, we compared the times of onset of contraction of the hemidiameters associated with each of 54 segments with the time of onset of contraction of the average of all the hemidiameters for the ventricular contour. In the second method we used a radial coordinate system and determined relative phase relationships by plotting the motion of each of 54 segments against the average motion of all segments.**

The resulting pattern showed that, on the average, the midregion of the inferior wall began to contract 25 msec before the apex and the midregion of the anterior wall began contraction 18 msec before the apex. In 12 of 25 patients the interior and anterior walls both began to contract before the apex. In only one of 25 patients did the apex begin to contract first. This sequence of contraction corresponds to the reported sequence of electrical activation for normal human left ventricles.

CONSIDERABLE EFFORT has been expended in studies in both animals[1-6] and humans[7-10] to determine whether the transverse or minor axis of the left ventricle initially increases during the preejection phase of systole (isovolumic contraction). Although only a limited number of true normal subjects has been studied, there is now general agreement that the transverse diameter of the endocardial cavity in humans decreases[7-9] during the preejection phase while the epicardial transverse diameter increases[10] because of muscle thickening. These results imply that the shape of the normal human ventricular cavity does not become more spherical during the preejection phase of systole.

The present study was performed to analyze in greater detail the temporal sequence of endocardial wall motion for individual segments and to determine whether a characteristic pattern exists for the sequence of onset of mechanical contraction of the normal human left ventricle.

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Methods

The 25 normal patients used in this study had 1) no valvular or congenital lesions, 2) no significant coronary artery lesions (less than 30% diameter reduction), 3) normal end-diastolic volumes and pressures, 4) normal ejection fractions, and 5) normal ECG or nonspecific ST-T wave changes. Twenty-one of the 25 patients had no evidence of coronary artery lesions by selective coronary arteriography. Four patients each had a single lesion in a single coronary artery — patients 14, 16 and 20 in the right coronary artery and patient 7 in the left anterior descending — none of which reduced the lumenal diameter more than 20–30%.

Before coronary arteriography we obtained left ventricular angiograms in the 30° RAO projection by injecting a 76% solution of meglumine diatrizoate at the rate of 15 ml/sec for 3 seconds. Using a 9-inch image intensifier, we recorded single-plane ventriculographic images at 60 frames/sec (16.7-msec intervals) on cine film, video disc and video tape with a simultaneous ECG tracing. We analyzed only normally conducted beats which did not follow an extra systole.

We analyzed the motion of multiple segments of the endocardial border of the left ventricular silhouette using two independently derived parameters, time of onset of contraction (TOC) and quadratic measure of asynchrony (QMA). To decrease the possibility that the results might be biased by the method of analysis, we obtained the parameters by using different methods for tracing the ventricular chamber contours

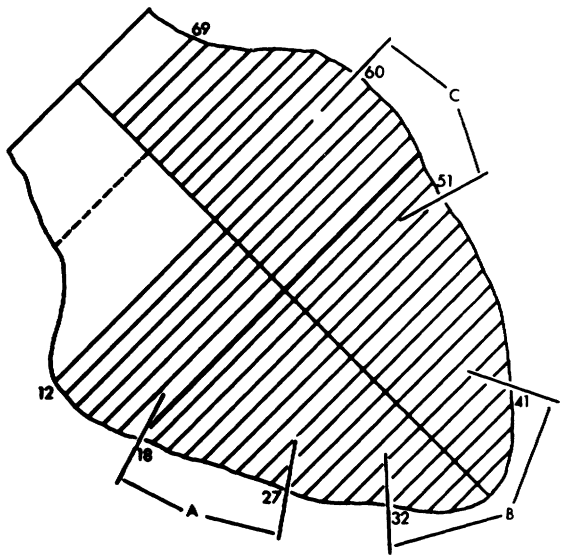

FIGURE 1. *The hemidiameter reference system used to analyze RAO ventriculograms. The 54 hemidiameters (16–69) were used for measuring segmental wall motion. The average parameter values for the hemidiameters within each of the regions A (18–27), B (32–41), and C (51–60) were compared to test the significance of the regional pattern for onset of contraction.*

and different reference systems for quantitative description of wall motion.

Method 1: Time of Onset of Contraction

In this method, using a sonic coordinate digitizer, we traced by hand from cine film the ventricular contours (16.7-msec intervals) from the eight frames immediately before and immediately after the R-wave peak. On each contour, a long axis was constructed as the line from the midpoint of the aortic valve plane to the apex. We formed hemidiameters by dividing the long axis into 36 equal parts and extending perpendicular chords from the long axis to define 54 segments on the ventricular contour which exclude regions associated with valvular structures (fig. 1). We obtained the time sequences for hemidiameter lengths at each segment and computed the average of all 54 hemidiameter lengths for each frame. To reduce the effects of noise generated in the tracing procedure, we smoothed the time sequences of hemidiameter lengths for each patient using a three-point, simple average. The length of each hemidiameter on a given contour was the average of its length on that contour and the contours immediately before and after. After smoothing, the sequence of contours was analyzed to identify the frame in which the maximum hemidiameter length for each segment occurred. The time of maximum hemidiameter length was called the TOC for that segment. Each segment's TOC was compared with a fiducial reference (the time at which the average hemidiameter reached its maximum) in order to determine whether the onset of contraction of a given segment preceded or followed the onset of contraction of the average hemidiameter. The number of frames by which the TOC of each hemidiameter led (contracted earlier) or lagged (contracted later) that of the average was used as a quantitative parameter to describe the time of onset of segmental contraction (fig. 2).

Method 2: Quadratic Measure of Asynchrony

To obtain the QMA, we determined the coordinates of the sequence of contours at 16.7-msec intervals throughout systole (peak of R wave to minimum ventricular volume) using automated border recognition techniques.[11] We used a radial coordinate system[12, 13] in which 72 radii were drawn at 5°-increments from the midpoint of the long axis (midpoint of aortic valve to apex) to the endocardial border for each contour.

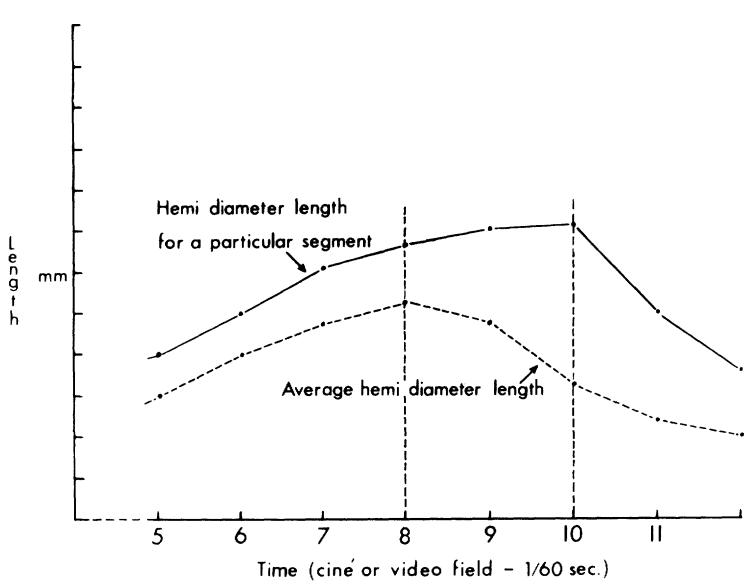

FIGURE 2. *The method by which the time of onset of contraction (TOC) parameter was derived. For each wall segment the time of maximum hemidiameter length (cine frame 10 in this example) was compared with the time of the maximum average of all 54 hemidiameter lengths (cine frame 8 in this example). The TOC value in this case would be −2, since the given segment reached its maximum hemidiameter length two cine frames after the maximum average.*

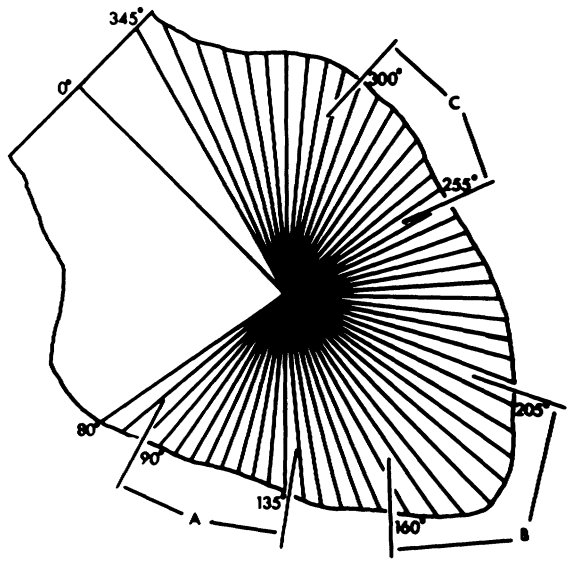

FIGURE 3. *The radial reference system used to generate the quadratic measure of asynchrony (QMA) parameter. The radii are drawn in 5°-increments from the midpoint of the long axis to the endocardial wall. The 54 radii from 80–345° were used for measuring segmental wall motion. The average parameter values for the radii within each of regions A (90–135), B (160–205) and C (255–300) were compared to test the significance of the regional pattern for QMA.*

We also determined an average of the radial lengths for each contour, using the 54 segments of the contour (fig. 3) not associated with valvular structures. For each angle, the radial lengths at that angle were plotted at 16.7-msec intervals on the vertical axis against the lengths of the average radius for the contour on the horizontal axis (fig. 4). In this method, the plot for a segment which does not contract synchronously with the average for the ventricle fails to show a linear relationship. A measure of the deviation from synchronous motion was obtained by fitting a parabola of the form $y = ax^2 + bx + c$ to the plot obtained for each segment. The variables x and y correspond to a coordinate system which has been translated and rotated so that the y-axis bisects the range of x values and is perpendicular to the linear regression slope. The coefficient of the quadratic term has units of cm^{-1} and its magnitude is dependent upon the range of x and y values as well as the shape of the curve. In each patient the range of x and y values is determined by ventricular size as well as the extent of contraction. To compensate for the effects of interpatient size differences, a scale factor equal to the magnitude (in centimeters) of contraction of the average radius for each patient was used to multiply the quadratic coefficient. This product, which was defined as QMA, is a normalized, dimensionless parameter determined solely by the shape of the curve. QMA had a positive sign (the parabola was concave upward) whenever the segment motion began or ended earlier or initially moved more rapidly than the average of all segments of the ventricle. Conversely the QMA was negative (parabola was concave downward) when a segment motion began or ended later than the average for the venrtricle. The QMA was calculated for all 54 segments in each of the 25 normal patients and an average value for each segment was computed. To insure that the results for the average pattern of onset of contraction were not determined by one or two anomalous patients, the mean and median values were compared at each segment.

The average patterns (determined by the mean parameter values at each segment of the ventricular contour) for TOC and QMA were compared to ascertain whether the resultant sequence for the onset of contraction was method dependent. Because the values of QMA or TOC at a given angle were not normally distributed, standard correlation procedures or a paired *t* test were not appropriate for this comparison. Therefore, we calculated the concordance between the two methods using a nonparametric statistical test (Kendall's tau).[14]

To determine whether there was a significant difference between the TOC in one region of the ventricular wall compared with the onset of contraction in another region, we calculated the average TOC and QMA for each patient for each of three regions. Region A was defined on the inferior endocardial wall by TOC segments 18–27 and QMA angles 90°–135°; region B on the apex by TOC segments 32–41 and QMA angles 160°–205°; and region C on the anterior endocardial wall by TOC segments 51–60 and QMA angles 255°–300° (figs. 1 and 3). Because of a wide range of values of QMA or TOC in a given region, we did not assume that the values for the set of patients would fit a given distribution. Therefore, we used a Wilcoxon signed rank[15] test to evaluate the significance of differences in the onset of contraction between these regions. We also examined the significance of the pattern of the sequence for the onset of contraction by plotting for each patient the difference between the parameter values in regions A and B on the vertical axis against the difference between regions C and B on the horizontal axis. From this plot, each patient was classified into one of four quadrants according to the relative sequence in which the onset of contraction in regions A, B and C occurred. We computed the chi-squared value for the difference between the actual distribution of patients in each quadrant and an expected distribution if the sequence of contraction was truly random.

Next, we examined the agreement between the two methods in individual patients by calculating the concordance between methods for each patient using Kendall's tau test.

Finally, we analyzed the reproducibility of the derived parameters and the sources of error which could contribute to discrepancies between the two methods. We used the difference in patient classification on the quadrant plot obtained by each method as a qualitative measure of the discrepancy between

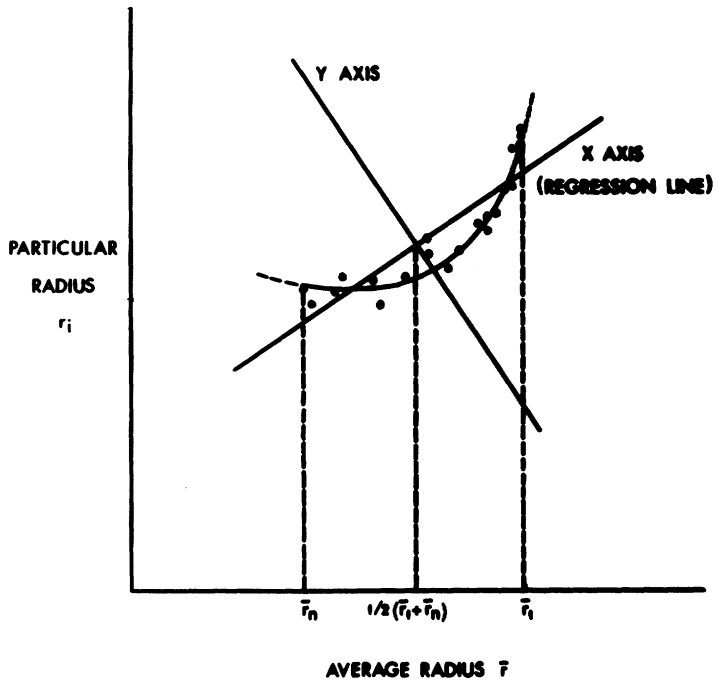

FIGURE 4. *The method by which the quadratic measure of asynchrony (QMA) parameter is determined. For each segment, the wall motion (vertical axis) is plotted against the average motion for the ventricle (horizontal axis) throughout systole. A parabola is fitted to this plot to allow measurement of the asynchrony. The value of the quadratic term of the parabola was normalized by multiplying by the difference between end-diastolic ($\bar{r}_1$) and end-systolic ($\bar{r}_n$) values of the average radius to obtain QMA.*

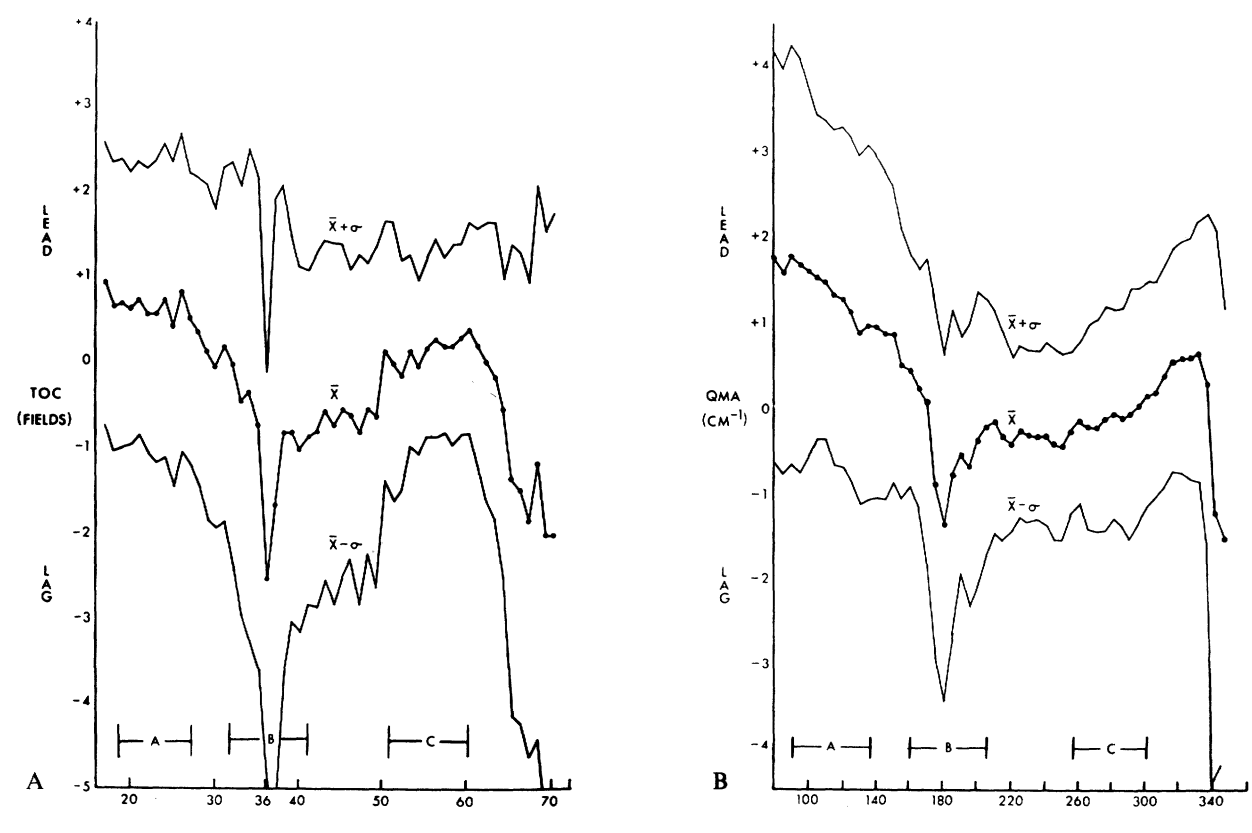

FIGURE 5. *A) The average time of onset of contraction (TOC) for 25 patients is plotted for each segment of the ventricular wall. The positive values between segments 18 and 27 (inferior wall) and 51 and 60 (anterior wall) show that those segments begin to contract earlier than the average for the ventricle. The negative values in the apical region (segments 32–41) indicate that this is the last area in which contraction begins. B) The average quadratic measure of asynchrony (QMA) for 25 patients is plotted for each segment of the ventricular wall. The positive values for regions of the inferior (segments 90–135°) and anterior (segments 255–300°) walls indicate that contraction in these regions begins earlier than at the apex (segments 160–205°).*

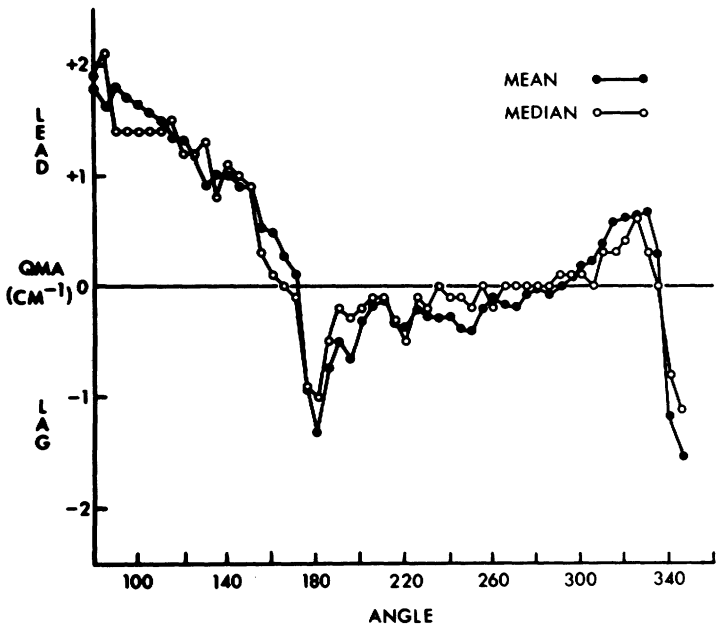

FIGURE 6. *A comparison of the mean and median values of the quadratic measure of asynchrony at each angle around the ventricular contour shows that despite the wide range of values, the characteristic pattern is not determined by individual outliers.*

methods. To test whether any discrepancy was due to the difference in reference systems (hemidiameter or radii) or the methods for tracing contours (manual vs automated), we reprocessed the ventricular contours for five patients a third time, using the automated videometry system, and determined the QMA and TOC parameters using the identical set of contours.

Results

The average values of TOC and QMA for the 25 normal patients are plotted for each segment of the endocardial contour (fig. 5). The values of TOC (fig. 5A) show, on the average, that the segments midway on the inferior wall (region A) start to contract 25 msec (1.5 cine frames) before the segments at the apex (region B). The segments in region C on the anterior wall begin to contract an average of 18 msec before the segments at the apex. The average QMA values (fig. 5B) confirm this same pattern, although the actual time relationships are not calculated by the QMA method. The average QMA value is positive for the segments on the inferior and anterior walls, indicating that the motion in these regions usually begins earlier than the average for the ventricle. Because the parameters varied widely between patients, the standard deviation has been plotted for both methods at each angle. The median value for QMA at each seg-

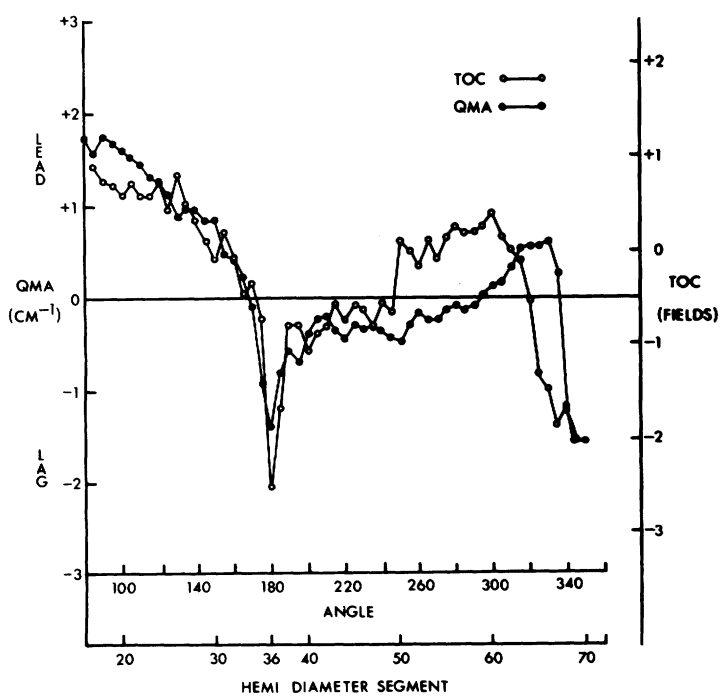

FIGURE 7. *The average quadratic measure of asynchrony and time of onset of contraction values for 25 patients are superimposed and plotted for each segment of the ventricular wall. Despite the different methods of analysis, the characteristic pattern which shows earliest contraction in the midregion of the inferior wall and latest contraction at the apex is consistent.*

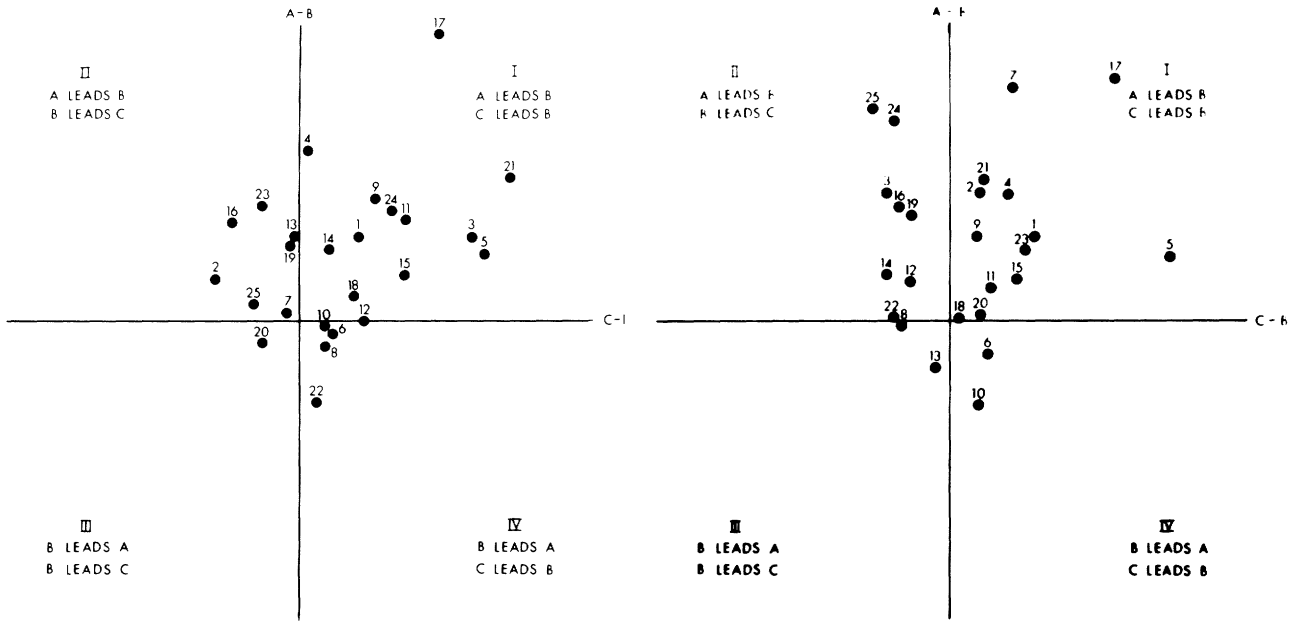

FIGURE 8. *A) For each patient, the difference between the times when region A (inferior wall) and region B (apex) start to contract is plotted on the vertical axis. The difference between onset of contraction at the midregion of the anterior wall (region C) and the apex is plotted on the horizontal axis. Thus for all patients in quadrant I of this plot, regions A and C both begin to contract before the apex. Patient 20 in quadrant III was the only case in which the apex began to contract earliest. B) In a plot similar to figure 8A, the average value of the quadratic measure of asynchrony (QMA) in region B (apex) is subtracted from the average value of QMA in region A (inferior wall) for each patient and plotted on the vertical axis. The difference in QMA between the anterior wall (region C) and apex is plotted on the horizontal axis. In only two cases (patients 8 and 13) did the apex begin to contract earlier than either of the other two regions.*

ment is given in figure 6. The close agreement between the median and mean values of QMA indicates that the distribution of values about the mean is symmetric and that the shape of the curve is not determined by individual outliers despite the wide range in values. Because of the discrete nature of the TOC parameter (values are an integer multiple of the 16.7-msec cine frame interval), it was not meaningful to compare the median values with the average values, as was done for QMA.

Figure 7 shows the agreement between the average patterns for the two methods when the TOC curve is scaled so that the variance and means for both curves in figure 5 are of equal magnitude. From Kendall's tau test for concordance, the probability that the average results of the two methods are not concordant is less than 0.001.

The results of the Wilcoxon signed rank test (used to determine whether the average values for the onset of contraction in regions A and C were significantly different from those for region B) are presented in table 1. The results by both methods show that the midportion of the inferior wall begins to contract significantly earlier than the apex. The difference between the anterior wall and the apex is less pronounced.

The activation sequences for each patient plotted by the TOC method are shown in figure 8A and by the QMA method in figure 8B. The vertical axes in these plots represent the difference between the average parameter values of the segments in regions A and B for each patient. The horizontal axes represent the differences between the average values for the segments in regions C and B. For example, in figure 8A, 48% (12 of 25) of the patients are in quadrant I, which means that by TOC, the onset of contraction occurred in both regions A (inferior wall) and C (anterior wall) before the apex (region B) started to contract. Only in patient 20 did the TOC method show that contraction began first at the apex (quadrant III). If the contractions originated randomly among the three regions, one would expect 8.33 patients to fall into quadrants I and III and 4.17 patients in quadrants II and III. A chi square test for the data shown in figure 8A indicates that the probability that the observed distribution was random is less than 0.0005. Figure 8B shows that, by the QMA method, only two patients exhibited a contraction sequence which originated in the apex, while in 13 cases regions A and C both began to contract before the apex. The probability that this distribution was random is less than 0.001. Thus, there appears to be a characteristic pattern for onset of contraction in which the transverse axis shortens before the long axis. This pattern is evident when one analyzes the group as a whole by either of two independent methods.

TABLE 1. *Probabilities That the Average Parameter Values for Onset of Contraction in Regions A (Inferior Wall), B (Apex), and C (Anterior Wall) are Significantly Different*

	A (inferior wall) vs B (apex)	B (apex) vs C (anterior wall)
QMA	$p < 0.001$	NS
TOC	$p < 0.001$	$p < 0.05$

Abbreviations: QMA = quadratic measure of asynchrony; TOC = time of onset of contraction.

As can be seen in figures 8A and 8B, comparing the two methods in an individual patient does not give the same level of agreement as when data for the group is analyzed. Table 2 summarizes how individual patients were classified by the QMA and TOC methods in figure 8. The numbers in this contingency table represent the number of patients classified in each of the four quadrants by each method. The sum of the diagonal elements shows that in 14 cases (56%) both methods gave the same classification. In patient 20 the QMA method classified the patient in quadrant I (apex is last region to contract) while the TOC method classified that patient in quadrant III (apex the first region to contract). A chi square contingency test on the data in table 2 shows that one can reject (at the $p < 0.05$ level) the hypothesis that the classification by the two methods is independent. We used Kendall's tau test for concordance to analyze the agreement of both parameter values at each angle for each patient. In 11 of 25 patients (44%), there was significant concordance between the methods, in one (4%) there was significant lack of concordance, and in 13 there was neither significant agreement nor disagreement.

Finally, in five patients the TOC and QMA parameters were recalculated from a third sequence of identical ventricular contours. The concordance between QMA and TOC values for the individual patients was significantly improved in four of the five patients. However, the agreement in classification according to the scheme in figure 8 was not improved by calculating both parameters from an identical set of contours.

Discussion

By two independent methods and a variety of supportive statistical tests we have shown that, in the normal human left ventricle, the transverse diameter of the endocardial cavity generally begins to shorten before the long axis of the ventricular chamber. Furthermore, a characteristic sequence for the onset of contraction exists in which the region on the inferior wall midway between the mitral valve and apex as seen in the RAO view begins to contract an average of 25 msec before the apex. The second region to contract is normally the midregion of the anterior wall, which begins to contract an average of 18 msec before the apex. This sequence is also evident in the data presented in a study by Gibson et al.,[16] although their work did not specifically evaluate the preejection phase of systole.

TABLE 2. *Contingency Table Showing the Relationship Between the Way Each Patient Was Classified by the Different Methods Shown in Figure 8*

	QMA			
TOC	I	II	III	IV
I	9	3	0	0
II	4	3	1	0
III	1	0	0	0
IV	0	1	1	2

Abbreviations: QMA = quadratic measure of asynchrony; TOC = time of onset of contraction.

Rushmer[2] reported that the canine ventricular cavity appeared to assume a more spherical configuration during the preejection phase of systole. However, other investigators have since shown in both closed-chest dogs[6] and normal humans[7-9] that the left ventricular chamber becomes more elliptical during preejection. However, in each of the human studies the number of true normals was relatively small, an important consideration because conditions such as atrial septal defect and mitral stenosis may affect factors responsible for changes during the preejection phase of systole.

Rushmer[1, 2, 5] and Hawthorne[3] reported that the interpretation of their results was limited by the experimental preparation they used, and noted differences in preejection contraction patterns between the open-chest and closed-chest canine preparations. Furthermore, they showed that alterations in preejection contraction patterns could be induced by altering the sequence of electrical activation with ventricular pacing and by alterations in end-diastolic volume. More recently, Rankin[6] and co-workers used more sophisticated measurement techniques than were available to earlier workers to confirm these observations. They noted that in the closed-chest dog the predominant geometrical change during isovolumic contraction was toward a more elliptical configuration. In contrast, in the open-chest dog the ventricular cavity tended to become more spherical during isovolumic contraction. By altering venous return in the closed-chest dog and by volume loading in the open-chest dog, they showed that the isovolumic contraction pattern becomes more spherical with diminishing ventricular volumes and more elliptical with increasing ventricular volumes. In addition, Rushmer[2] and Streeter and Hanna[17, 18] pointed to the role of myocardial fiber orientation as a determinant of changes in ventricular geometry. Thus, on the basis of canine studies, it appears that any observed sequence of segmental contraction during the preejection phase of systole is the net result of a complex interaction of factors such as the sequence of electrical activation, ventricular size (preload) and myocardial fiber orientation. Furthermore, the relative importance of one of these factors may change if another is altered or if the basic properties of the myocardium itself are affected by a disease process.

Durrer[19] and co-workers reported that the earliest

electrical activation of the endocardial surface of the normal human left ventricle occurs at regions A and C as defined in this paper and at one additional site on the interventricular septum which is not visualized in the RAO projection. Although they saw considerable variation among individual hearts, the apical region was generally the last area of the endocardium to be electrically activated. When these data are combined with the results of our study, it is plausible to speculate that in the normal ventricle the sequence of electrical activation may play the major role in determining the onset of segmental contraction. The individual variability that we encountered might have been due to variability in electrical activation or other factors (ventricular volume and fiber orientation) which play important roles in determining ventricular geometry. Because we did not alter the sequence of electrical activation or the ventricular volume in this study, we could not directly evaluate the relationship between electrical and geometric factors.

Recent studies[10-24] have described early regional asynchronous contraction (tardokinesis) which has been ascribed to regional differences in myocardial contractility secondary to ischemic heart disease. Our study and the experimental studies of Rushmer,[1, 2, 5] Hawthorne,[3] Rankin et al.[6] and others suggest that such a simplistic explanation may not be entirely valid. However, further investigation of the phase relationships of the contraction of the human left ventricle should provide additional information for understanding the complex relationship between the factors which determine both the time course and the magnitude of segmental contraction. Because the muscular structure and the wall thickness are different in the apex of the ventricle from those in the main body of the chamber, and because the entire myocardium is not activated simultaneously, the temporal geometric influence on the contraction pattern of the ventricle is difficult to evaluate. Muscle which is activated relatively late in systole must contract against higher ventricular pressures than those segments activated early.[4, 25] It requires up to 60 msec from the time the intraventricular septum is activated until the entire myocardium is depolarized and up to 30 msec for the activation impulse to spread from the endocardium through the irregular structure of the syncytium to the epicardium.[4, 19] These time periods are of the same order of magnitude as a period of isovolumic contraction (60 msec) described by Rushmer.[1]

Although general patterns were identified for group data in our study, there was a significant variation between patients and methods. As noted above, important sources of variability could have been variation in the electrical activation sequence, ventricular volume and fiber orientation. Another obvious source of variability is the inherent error involved in tracing angiographic contours. Previous work[26] has shown that there are often (8% of all regions) significant differences between the way in which different observers trace the contours of the same beat when end-diastolic and end-systolic contours are examined. If an uncertainty of 1 mm exists when one traces end-diastolic and end-systolic contours, the resulting error (10%, assuming a typical wall motion of 1 cm) is marginally acceptable. When multiple contours throughout the systole are used to generate wall motion parameters, the 1-mm error in contour tracing could generate a 200% error (assuming that the movement during each 16.7-msec interval is approximately 0.5 mm).

Variability could also be caused by rotation of the ventricle in the chest cavity. Rotation out of the plane normal to the x-ray beam would create a false impression of movement. Because the TOC measurements concern only the onset of contraction rather than complete systole, the rotation effect could be expected to be minimal, although of unknown magnitude.

In conclusion, we have documented a characteristic sequence for the onset of segmental endocardial contraction in which the inferior wall leads the anterior wall and the apex is generally the last region to contract. Both analytical methods used in this paper appear to provide sensitive parameters by which the temporal relationships of segmental contraction can be evaluated. However, before the QMA and TOC parameters can be used to detect pathologic states, reproducibility in contour determination must be improved, and additional studies to define the degree of physiological variability must be performed.

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Determinants of Ventricular Function in Pressure-Overload Hypertrophy in Man

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SUMMARY **To test the hypothesis that impaired cardiac performance in some patients with pressure-overload hypertrophy is due to inappropriately high wall stress, rather than depressed contractility, the importance of hemodynamic and geometric factors was assessed in 14 patients with isolated aortic stenosis and various degrees of left ventricular failure (ejection fraction range 0.19–0.85). There was poor correlation between either aortic valve area, peak left ventricular systolic pressure, or left ventricular mass, and measures of ventricular function. In contrast, there were close correlations between circumferential wall stress and both ejection fraction ($r = 0.96$) and velocity of fiber shortening ($r = 0.91$) in patients with aortic stenosis. Force-velocity-shortening relationships in six normal control subjects fell on the same regression line as that defined by the patients with aortic stenosis, while force-velocity-shortening relationships of patients with primary myocardial failure clearly differed. A major determinant of wall stress was the ratio of left ventricular wall thickness to cavity radius (h/R). Patients with h/R ratios > 0.36 had higher values for ejection fraction (0.61 ± 0.06 vs 0.36 ± 0.07, $p < 0.05$), Vcf (0.79 ± 0.10 vs 0.39 ± 0.04 sec^{-1}, $p < 0.05$) and stroke work index (71 ± 10 vs 45 ± 9 g-m/m^2, $p < 0.005$) than those with lower ratios.**

The results indicate that left ventricular wall thickness and geometry are closely correlated with ventricular performance in patients with pressure-overload hypertrophy due to aortic stenosis. Poor cardiac performance in some such patients may be due to inadequate hypertrophy (or inappropriate geometry) rather than to depression of myocardial contractility.

MYOCARDIAL FUNCTION in pressure-overload hypertrophy is a controversial subject. It is generally agreed that the development of hypertrophy in response to a pressure overload is associated at least initially with wall thickening commensurate with the increased systolic pressure, tending to normalize myocardial wall stress.[1, 2] Although this increased muscle mass may allow more normal ventricular function by maintaining output against the increased resistance, intrinsic contractile properties of the hypertrophied muscle, especially in man, are not clearly defined. While earlier studies with papillary muscles from animals with experimentally-induced ventricular hypertrophy showed a decrease in myocardial contractility,[3, 4] subsequent investigators have noted only a transient decrease, followed by a return to normal over several weeks.[5] Similar conflicting data have been reported for intact hearts.[6, 7]

In man, the development of clinical cardiac decompensation in the course of pressure-overload hypertrophy has been attributed to a depression in contractility.[8] Levine et al.[9] found that normal indices

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