Diastolic Biomechanics in Normal Infants Utilizing MRI Tissue Tagging

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Background—Most of what is known about diastolic function in normal infants is derived from flow and pressure measurements. Little is known about regional diastolic strain and wall motion.

Methods and Results—Magnetic resonance tissue tagging was performed in 11 normal infants to determine regional diastolic strain and wall motion. Tracking diastolic motion of the intersection points and finite strain analysis yielded regional rotation, radial displacement, and $E_1$ and $E_2$ strains at 3 short-axis levels (significance was defined as $P<0.05$). $E_2$ “circumferential lengthening” strains were significantly greater at the lateral wall, regardless of short-axis level, whereas $E_1$ “radial thinning” strains were similar in all wall regions at all short-axis levels. In general, no differences were noted in strain dispersion within a wall region or in endocardial/epicardial strain at all short-axis levels. At all short-axis levels, septal radial motion was significantly less than in other wall regions. No significant differences in radial wall motion between short-axis levels were noted. Rotation was significantly greater at the apical short-axis level in all wall regions than in other short-axis levels, and it was clockwise. At the atroioventricular valve, septal and anterior walls rotated slightly clockwise, whereas the lateral and inferior walls rotated counterclockwise.

Conclusions—Diastolic biomechanics in infants are not homogeneous. The lateral walls are affected most by strain, and the septal walls undergo the least radial wall motion. Apical walls undergo the most rotation. These normal data may help in the understanding of diastolic dysfunction in infants with congenital heart disease. (Circulation. 2000;102:218-224.)

Key Words: rotation ■ diastole ■ biomechanics ■ infant ■ magnetic resonance imaging

Although diastolic function has been studied less than systolic function, it has recently gained increasing attention in the literature. The lusitropic state of the heart in children is important in many disease states, including hypertrophic cardiomyopathy, hypertension, patients on dialysis and after kidney transplantation, infants of diabetic mothers, anthracycline cardiotoxicity, and in cardiac transplant rejection. It has been studied in a myriad of congenital heart diseases—such as hypoplastic left heart syndrome, and after tetralogy of Fallot, aortic coarctation, and Fontan repair. Most diastolic studies in children have used echocardiographically based procedures (eg, Doppler echocardiography automated border detection or Doppler tissue imaging) or angiography and looked at flow rates, chamber dimensions, or pressure-based measures. Few studies have used MRI to evaluate flow in diastole, and none have assessed strain and regional wall motion with MRI in children.

Studies describing the flow patterns in normal children are key in understanding the altered diastolic function in disease states. Similarly, understanding the normal diastolic patterns of strain and regional wall motion is another important step forward. Little is known of these normal diastolic patterns in infants, and the present study was undertaken to determine this using MRI tissue tagging (specifically, spatial modulation of magnetization [SPAMM]).

Methods

Patients

Eleven subjects with normal hearts who were undergoing MRI to evaluate vascular rings at the Children’s Hospital of Philadelphia between June 1, 1996, and January 31, 1997, were prospectively studied. All patients were clinically well from a cardiovascular standpoint. The subjects ranged in age from 2 to 11 months, with a mean of 6.2 ± 2.1 months (median, 8.4 months). Mean heart rate was 120 ± 21 beats per minute. Subjects had to be able to undergo a 1-hour MRI scan under sedation. All patients were in normal sinus rhythm and had no evidence on surface ECG of altered electrical activation. No patient had any arrhythmia that precluded study in the scanner. All patients fasted 4 hours before MRI.

MRI

Studies were performed on a Siemens 1.5 Tesla Vision system. All patients were monitored with pulse oxymetry, ECG, and by direct visualization via television. Our scanning protocol for systole has

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Figure 1. SPAMM imaging and image analysis. The images are oriented such that the right side is anatomically right and anterior, the left side is anatomically left and posterior, the top of the image is anatomically superior, and the bottom of the image is anatomically inferior. Six SPAMM images were obtained throughout diastole (upper left panel), and the intersection points were tracked. Delaunay triangulation was used to create a triangular grid automatically from the intersections, and the centroid of each triangle was used to compute regional wall motion (lower right panel). Dots represent the end-diastolic triangular centroid location, and the tails represent the subsequent rotation. Two-dimensional finite strains were computed by measuring triangle deformation. The data are coded in gray-scale (lower left panel is the E2 strain map) and superposed onto the anatomic image (upper right panel). White areas represent regions of most circumferential shortening, whereas darker gray and black areas are regions of least circumferential shortening.

The type of tissue tagging used in this study was the SPAMM technique. Briefly, SPAMM imaging makes use of a prepulse sequence, applied immediately after the R wave, which saturates 2 series of parallel stripes perpendicular to each other (generated by 5 radiofrequency pulses separated by field gradients). In-plane cardiac movement displaces and distorts these “cubes of magnetization” and tracking this motion enables the measurement of strain and wall motion. We acquired 6 gradient-echo images throughout diastole starting immediately after the SPAMM prepulse with the following parameters: repetition time was the R-R interval (range, 300 to 650 ms), the flip angle was 30°, thickness was 4 to 7 mm, inversion time was 16 ms, the number of excitations was 2, the matrix size was 256×256, and the field of view was 160 to 250 mm. End-diastole was determined by the R wave on ECG. The separation of the grid lines was selected to allow 2 to 3 lines between endocardial and epicardial surfaces (ie, 3 to 4 rows of cubes). Black band (tag) width was ~1 to 1.5 mm.

Image and Data Analysis
Images were analyzed on a Sun SPARC 10 workstation (Sun Microsystems) using the VIDA (Volumetric Image Display and Analysis) software package. Evaluation of wall motion and strain has also been previously described,18–20 and the Appendix in our previous investigation details the mathematics of strain calculations.19 In brief, the initial step was to track the magnetically tagged grid intersections through diastole. Delaunay triangulation25 was used to create the triangular grid automatically from the intersections, providing uniform, nonoverlapping triangles. The centroid of each triangle was used to compute regional wall motion. The regional deformations of the myocardium were then characterized using homogeneous finite strain analysis on the deforming triangles.18–20,28–31 This methodology has been validated in a phantom study and was used in vivo by Young et al. These studies demonstrated that homogeneous strain analysis produced unbiased estimates of the principal strains, principal angles, and orientations of the principal axes.

Wall Motion
As described previously,18–20 the elements used in calculating wall motion in 2 dimensions include the (x, y) coordinates of the centroid of all triangles for each diastolic image and the ventricular cavity centroid based on the endocardial border (Figure 1).

Rotation and radial lengthening were then measured using the motion of the centroid of the triangles relative to the centroid of the ventricular cavity. How far the muscle moved away from the ventricular cavity centroid (radial motion) from phase n to phase n + 1 (where n increases as diastole progresses) is described by equation 1.

\[
\frac{1}{h_1} \left[ \left| \mathbf{P}_{n+1} - \mathbf{P}_n \right| - \left| \mathbf{P}_n - \mathbf{P}_{n-1} \right| \right] = \sqrt{(x_{n+1} - x_n)^2 + (y_{n+1} - y_n)^2} \left( (x_n - x_{n+1})^2 + (y_n - y_{n+1})^2 \right)^{-1/2}
\]

In this equation, (x, y) and (x_{n+1}, y_{n+1}) were the coordinates of the centroid of the triangle at phases n and n+1, respectively, (x, y) were the coordinates of the ventricular cavity centroid, and P, and P_{n-1} were the lengths of the vectors from the ventricular cavity centroid to the centroid of triangle at phase n and n+1, respectively. Radial motion was taken as the net outward motion of the centroid of each triangle away from the ventricular cavity centroid relative to the end-diastolic distance (measured in pixels of distance moved divided by end-diastolic radial length to normalize for heart size). By convention, radial motion outward was negative and motion inward was positive, as previously described.19–20

Rotation was calculated by finding the angle θ made by 2 vectors drawn from the ventricular cavity centroid to the centroid of the triangle at phases n and n+1, as described in equation 2.

\[
\cos^{-1}\left( \frac{\mathbf{P}_n \cdot \mathbf{P}_{n+1}}{\left| \mathbf{P}_n \right| \left| \mathbf{P}_{n+1} \right|} \right)
\]

In this equation, P, and P_{n+1} were vectors (\left| \mathbf{P}_n \right| and \left| \mathbf{P}_{n+1} \right| were the length of those vectors) from the ventricular cavity centroid to the centroid of the triangle at phases n and n+1, respectively, P \cdot P_{n+1} was the vector dot product. Net rotation (rotation measured from end-systole to end-diastole, sampling at 6 time points) was quantified for magnitude and direction. By convention, clockwise motion was negative and counterclockwise motion was positive for viewing the heart from apex to base.

The definition of twist in the literature is controversial. Some investigators define twist as a rotation of one plane relative to another,25 and others define twist as a rotation of the plane with “respect to their initial positions and the center of gravity.” This study measures the latter, which we term rotation.
Wall motion data were displayed graphically (see Figure 1). Dots are the location of the centroid of the triangle at end-systole, and tails represent the subsequent motion in diastole. The myocardial wall was divided into standard anatomic regions (septal, inferior, lateral, and anterior walls) using the papillary muscles and other anatomic landmarks from the transverse images as references to perform the analysis.

**Homogeneous Finite Strain Analysis**

This study uses a 2D strain approach (Figure 1). The mathematics of the homogeneous strain analysis is outlined in the Appendix of our previous investigation. Briefly, the complex deformation patterns of the myocardium, as described by continuum mechanics, have been used by us and others. This approach assumes that deformations within each triangle relative to end-systole are locally homogeneous; this is similar to the assumption made by Azhari et al. After a Lagrangian (Green’s) strain tensor, $E$, was computed for each triangle, the strain tensors were diagonalized to be independent of any coordinate system. The local deformations were described by 2 principal strains ($E_1$ and $E_2$) and the orientation of the principal axes relative to the original coordinate system.

The first principal strain, $E_1$, was defined as the most negative strain, and the second principal strain, $E_2$, which was orthogonal to $E_1$, was defined as the most positive strain. In diastole, $E_1$ can be thought of as the “radial thinning” strain, whereas $E_2$ can be thought of as the “circumferential lengthening” strain. Strain values reported in this study were obtained by averaging the strain of all the triangles within the region. Strain values are reported as mean $\pm$ SD. Our research focused on the maximum negative ($E_1$) or positive ($E_2$) average diastolic strain in each region that occurred at end-diastole. The data were quantified and displayed for qualitative analysis in gray-scale form superimposed onto the anatomic images (Figure 1).

**Statistics**

Comparisons between 2 means and a mean with a hypothesized value were made using the unpaired, 2-way or 1-way Student’s t test and the Wilcoxon ranked sum test. Differences between various groups of subjects and locations (regional wall location using short-axis slices from base, mid, or apex) were analyzed by 2-factor ANOVA; repeated measures were used when appropriate. Comparisons between multiple means within groups was done with 1-way ANOVA; pairwise comparisons were made using Dunnett’s test or the Tukey-Kramer honestly significant difference test. All measurements are defined as mean $\pm$ SD. Intraobserver variability was determined by replicate measures and used Student’s t test. A single, trained observer performed all image analysis steps. Significance was defined as $P<0.05$. Statistical analysis was performed using JMP software, version 3.1.4 (SAS Institute).

To obtain the homogeneity of strain within the region (ie, the dispersion of strain within an entire wall region), the coefficient of variation was used; this used the SD of all the strains within a given region indexed to the average of all strains, as follows:

$$\text{Coefficient of variation} = \frac{\text{SD}}{\text{average}}$$

**Results**

In each category (strain and wall motion), data are grouped according to short-axis level (atrioventricular valve, mid, and apical), anatomic quadrant (anterior, inferior, posterior, and superior walls) and, of course, subject group. Coefficient of variation for strain measurements was $6.4\pm2.8\%$.

**Absolute Strain Measures**

$E_1$ Strain

Figure 2A displays strain data in gray-scale form superimposed on the anatomic image, and Figure 2B displays the principal circumferential lengthening strain in graphic format. The lateral wall had significantly higher $E_1$ strains than other wall regions at all 3 short-axis levels ($P<0.05$). No differences were noted between short-axis level for any anatomic wall region.

$E_2$ Strain

Figure 3A displays strain data in gray-scale form superimposed on the anatomic image, and Figure 3B displays the principal radial thinning strain in graphic format. No significant differences between anatomic wall regions were noted within short-axis levels, nor were significant differences noted between short-axis level for anatomic walls.
Distribution of Strain

**Homogeneity of Strain Within a Given Anatomic Region**

Only the inferior wall at the atrioventricular valve level differed (more heterogeneous) in the distribution of $E_2$ strains when compared with the other 3 wall regions at that level. Otherwise, at the atrioventricular valve, mid, or apical short-axis levels, no significant differences were noted in $E_2$ (Figure 4A) or $E_1$ strains (Figure 4B) between anatomic wall regions within a short-axis level, nor were significant differences noted between short-axis level for each anatomic wall.

**Radial Motion**

Figure 5A also depicts the radial motion in the short axis of normal infants in a graphic format, and Figure 5C displays the data quantitatively. Intraobserver variability was 6.1 ± 2.8%. At all short-axis levels, the septal wall moved significantly less outward from the centroid of the ventricular cavity than...
Diastolic wall motion data of the normal infant displayed (A) graphically and (B and C) quantitatively. A, On the left side of the figure, the image of the atrioventricular valve (AVV) short-axis plane is on top, the mid short-axis plane is in the middle, and the apical short-axis plane (APEX) is on the bottom. Orientation is as in Figure 1. Dots represent the end-systolic (ES) triangle centroid location, and the tails represent the subsequent motion. Note the limited septal wall motion compared with the other wall regions across all 3 short-axis levels. B, Quantitative diastolic net rotation for normal infants. Values are in degrees. Positive values indicate counterclockwise motion, and negative values indicate clockwise motion. Error bars represent SD. *At the atrioventricular valve short-axis level, significantly greater clockwise (negative) rotation existed at the septal and anterior walls when compared with the inferior and lateral walls, which rotated counterclockwise (positive). †Significantly greater clockwise (negative) rotation existed at the septal, lateral, and inferior walls at the apical short-axis level when compared with similar walls at the atrioventricular valve short-axis level. C, Quantitative diastolic radial wall motion data for normal infants. Values are in millimeters of movement indexed to end-diastolic radius (also in millimeters; mm ED diameter). Positive values indicate inward motion, and negative values, outward motion. Error bars represent SD. *Regardless of the short-axis level, the septal wall demonstrated significantly less outward radial wall motion than the other 3 wall regions.

**Discussion**

The increasing realization that diastole is of great importance is borne out by the progressively increasing amount of literature on the subject. Not only do diastolic parameters change in various disease states, but the administration of medication may unintentionally alter diastole adversely or enhance diastolic performance. Some authors have even suggested that some parameters of diastole correlate with morbidity and mortality. The complexity of diastolic function (eg, the role of restoring forces) underlies the need for a comprehensive understanding of normal diastolic function, which may aid in the medical and surgical management of patients with disease.

In pediatrics, the task of elucidating normal diastolic parameters is made more complex by the changing nature of the heart with growth and development. In 1995, Harada et al demonstrated that both peak E and the flow velocity integral of early diastole increased to reach the levels of older children at the age of 36 months, and these measurements leveled off thereafter. Both Bu’Lock et al and Schmitz et al also observed a change in Doppler-derived diastolic indices with age, especially with the early filling phase of diastole; their findings were consistent with those of Harada et al. In 1998, Harada et al published data demonstrating that in infants, the mass/volume ratio was increased and the peak E wave was decreased when compared with those of children aged 1 to 3 years. Because of the overwhelming evidence that infant diastolic mechanics are different from those of older children and adolescents, we limited our study population to infants (<1 year of age).

The diastolic properties of the heart are based on a number of complex, interrelated events, including loading conditions, speed and synchrony of myocardial relaxation, the viscoelastic properties of the ventricle, ventricular-ventricular interactions, and pericardial restraint, to name a few. The most important finding of this study is that infant diastolic mechanics are not homogenous throughout the short axis of the left ventricle; this is consistent with the emerging notion of “nonuniformity” of the heart in both systolic and diastolic function. Among the mechanisms for nonuniformity is asymmetric geometry of the heart, with the right ventricle overriding the left ventricle; this affects septal motion and contraction with respect to the lateral wall. Regional differences exist in the E/E’ circumferential lengthening strain, the distribution within a wall region, and radial wall motion and rotation. This is consistent with the nonuniformity of diastolic untwisting found in the dog by Rademakers et al.

As mentioned earlier, diastole is a very complex mechanical function for the ventricle. Active mechanisms are involved in relaxing the ventricle (eg, active transport of calcium into the sarcoplasmic reticulum), and passive mechanisms are also at work (eg, including some directly related to systole (eg, ventricular twisting in systole storing potential energy for untwisting and “suction” of blood into the ventricle in diastole). Regional differences may exist in, for
example, transport mechanisms of calcium in the developing infant; these mechanisms may not mature until later on in childhood, and they may explain these findings. In addition, regional systolic ventricular rotation may also be altered in the developing infant; this may account for the diastolic findings of our study.

It is well known that the right ventricles of newborn infants are hypertrophied compared with those of older children and adults. This is thought to be due to the systemic pressure and resistance the right ventricle faces with the patent ductus arteriosus. This hypertrophy recedes over a matter of months, with a concomitant change in fiber architecture. We know that (1) ventricular-ventricular interaction occurs in diastole,45 (2) alterations in right ventricular mechanics affect the left ventricle,46 (3) the right and left ventricles share the septal wall, and (4) the myocardium is a "syncytium of muscle fibers tethered within a collagen network,"47 with muscle fibers in continuity between the right and left ventricles.48 Thus, it is certainly possible that the right ventricular changes occurring during infancy have a mechanical effect on the diastolic properties of the left ventricle. The recent study by Stuber et al33 bears on this issue; it demonstrated (using MRI and the SPAMM technique) that patients with left ventricular hypertrophy due to aortic stenosis had greater untwisting velocities and prolongation of untwisting when compared with normal individuals.33

Strain
This study demonstrated that in the infant left ventricle, the only real mechanically significant difference (from a strain standpoint) was the higher circumferential lengthening strain ($E_2$) at the lateral wall in all 3 short-axis levels; the differences in strain in the other 3 wall regions were not significant. The lateral wall is the farthest away from the right ventricle; it is not "tethered" by the right ventricle, and it does not share a wall with the right ventricle, as is the case with the septal wall.41 This may be the explanation for this finding.

It should be noted that the radial thinning strain ($E_r$) and the heterogeneity of both types of strain within a given region (with the exception of the inferior wall at the atroventricular valve level) and along the long axis of the ventricle did not differ between wall regions.

Wall Motion
As mentioned above, the most striking finding in this study is that wall regions do not move similarly. In general, it was noted that rotation became more clockwise (negative) when moving from the atroventricular valve to the apex (eg, the inferior, lateral, and anterior walls rotated significantly more clockwise at the apical level than at the atroventricular valve level). This rotation, by being more pronounced at the apical rather than the atroventricular valve short-axis level, was consistent with the notion that the myocardium is less tethered at the apex than at the atroventricular valve level, where the atroventricular valve fibrous rings may play a role.

Although not statistically significant, a trend existed at all short-axis levels for the anterior wall region to do the most clockwise rotation. This is consistent with the findings of Rademakers et al42 in the dog, in which the percent of untwisting "was significantly greater in the anterior wall region" when compared with the other wall regions.

In addition, our study demonstrated that the septal wall, regardless of short-axis level, moved significantly less outward from the ventricular cavity than did the other wall regions. The explanation may be that both ventricles share the septal wall, and the ventricular-ventricular interaction with the hypertrophied infant right ventricle plays a significant role.45–48 Another explanation may lie in the fact that the left ventricular septal wall is morphologically different from the free walls in normal individuals.49 The free wall is thickest at the base, and then gradually tapers toward the apex. Compare this with the septum, where "a rounded peak" is formed "at its basal summit, becomes thickest at its midportion," and then, "after thinning a bit, the septum remains relatively constant in thickness and tapers only as it fuses with the apical portion of the free wall."49 This fact likely plays a role in explaining the behavior of the septum.

Limitations
In previous reports,18–20 we discussed in great detail the limitations of acquiring data in fixed planes, as was done in this study. Again, it must be noted that because our study deals with slices that are thick relative to the amount of through-plane motion (as would be anticipated in infants), it is thought that this limitation would not have an appreciable effect on the findings.

In addition, as our recent reports have previously discussed,20 2D strain analyses are inherently limited because they exclude the remaining components of the 3D strain tensor as used, for example, by Azhari et al.24 As also noted, however, solutions to 3D strain analysis require a priori knowledge of the deformation to interpolate the data that itself is dependent on assumptions. This may introduce error into the calculations.

As was noted above, this study used homogeneous strain analysis, which assumes that deformation is constant within a given unit. Strains, however, have been known to have some transmural variation. This, therefore, represents the limit of resolution.

Conclusions
Diastolic biomechanics in infants are not homogeneous. The lateral wall undergoes more wall thinning strain than other walls. The apical walls were observed to do the most rotation, and rotation in general became more clockwise when moving from base to apex. The septal walls at each short-axis level underwent the least radial wall motion when compared with other wall regions. These normal data may lay the groundwork for future studies into diastolic dysfunction in infants with congenital heart disease.

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References
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