METHODS

Patterns of Regional Diastolic Function in the Normal Human Left Ventricle: An Ultrafast Computed Tomographic Study

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The detailed evaluation of regional diastolic filling at multiple ventricular levels in the normal human left ventricle has not previously been reported. Ultrafast computed tomography was used to characterize global and regional early diastolic filling in the left ventricle of 11 normal male volunteers. Regional early diastolic filling data from six distinct ventricular levels (apex to base) were fit to a third-order polynomial curve, and the peak rate of diastolic filling and time of peak filling were determined. Peak filling rate was 259 ± 17 ml/s (±SEM) as a global average, where peak filling rate referenced to end-diastolic volume and stroke volume across the levels examined was 3.78 ± 0.17 s⁻¹ and 4.83 ± 0.20 s⁻¹, respectively. Average filling fraction was 39 ± 1%, and time to peak filling from end-systole was 145 ± 5 ms.

Regional (tomographic) peak filling rates, except for the most apical level examined, were not statistically different across the ventricle. Filling fraction and time to peak filling were remarkably constant from one level to another. However, reference of regional peak filling rate to regional end-diastolic volume demonstrated significant nonuniformity from apex (120% of average for all levels) to base (87% of average for all levels). Peak filling rate referenced to tomographic stroke volume was less variable and not statistically different across the ventricle as a whole.

In conclusion, values of regional absolute early peak diastolic ventricular filling rate or values normalized for regional end-diastolic volume are characteristically nonuniform across the left ventricle, whereas other variables such as filling fraction, time to peak filling and regional peak filling rate referenced to regional stroke volume are highly uniform. This confirms an intimate relation between rates of regional diastolic filling and regional ventricular size and stroke volume in the normal human heart.

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regional function across the left ventricle, insufficiencies or inaccuracies in the methods employed could seriously influence the results.

None of the previously mentioned cardiac imaging modalities, with the potential exception of two-dimensional echocardiography, provide high temporal and spatial resolution images to allow for detailed analysis of absolute ventricular volumes within a given region of the left ventricle. However, it is difficult to use echocardiography to fully assess regional diastolic function at multiple levels across the left ventricle in humans because of limited acoustic windows. Additionally, the images are not parallel to each other. The patterns of regional diastolic function in normal persons have not been previously fully evaluated. Characterization of pathologic diastolic function when systolic function or ventricular size is not adequately or clearly defined may underlie much of the confusion regarding results from prior investigations.

Ultrafast computed tomography (CT) has been extensively validated for use in measuring left ventricular mass and volumes in animals and humans, with errors of <5% (17-19). Additionally, it has been used for detailed analysis of normal left ventricular systolic function (20) and abnormal regional systolic function during acute infarction in the experimental laboratory (21,22) and during exercise in patients with coronary heart disease (23). In the current study we employed the multimodographic, minimally invasive, parallel imaging attribute of ultrafast computed tomography to evaluate patterns of regional left ventricular diastolic filling in the normal human left ventricle. Defining these patterns and characterizing potential variability between regions may allow for a better understanding of diastolic function in patients with a variety of cardiac diseases.

Methods

Ultrafast computed tomography. The mechanics of ultrafast computed tomography (Imatron C-100) have been described elsewhere (17-19). Briefly, this fourth generation scanner employs a magnetically deflected electronic beam that sweeps across one to four semicircular (210°) tungsten targets that surround the subject producing dual level tomographic scans in 50 ms. Up to 80 scans from any combination of these contiguous targets can be taken during a single injection of iodinated contrast medium. Slice thickness of each tomogram is 8 mm. Electrocardiographic (ECG) triggering on the peak of the R wave allows serial acquisition of data at a rate of 17 frames/s commencing at end-diastole. Commercially available off-line image analysis software allows for accurate placement of cardiac borders (17) and quantitation of tomographic and global left ventricular volumes (18,19,21) and function (20,22,23).

Study subjects. Initial studies were performed on 11 healthy male volunteers (aged 21 to 36 years, mean age 23 ± 4) who had no evidence of cardiac disease by history, physical examination, ECG or two-dimensional echocardiography. All subjects gave informed consent and were studied in compliance with a protocol previously approved by the University of Iowa Human Subjects Committee.

Data acquisition. No premedications were administered, and the subjects were instructed to fast for ≥4 h before the study. Self-adhering electrode pads were placed on the chest wall to allow for continuous ECG monitoring as well as triggering of the scanner. An 18 gauge, 2 in. (5.08 cm) intravenous catheter was placed in a right antecubital vein. The subjects were positioned in the scanner to facilitate acquisition of short-axis (transverse) tomograms from cardiac apex to base (20,24). Localization scans were obtained to determine the level of the left ventricular apex. The subject was then mechanically moved into the scanner to assure that the most caudad tomographic image was obtained at the level of the cardiac apex. This assured that all subjects would be subsequently imaged in a uniform fashion.

Once the patient was positioned, circulation time was estimated during normal respiration after administration of a bolus injection of 10 ml of a dilute solution of magnesium sulfate (0.2%). This estimation of circulation time facilitates accurate timing of the contrast injection and scanning sequence. A powered injector delivered an infusion of iodinated contrast medium (meglumine diatrizoate) at 0.35 ml/kg for a time interval roughly equal to the estimated circulation time plus 3 to 4 s. Scanning commenced at the "circulation time." This method of contrast delivery assured that adequate ventricular opacification would be present throughout the scanning sequence. Immediately before scanning, the subject was instructed to breathe normally and to suspend respirations at roughly one-half normal inspiratory volume approximately 5 to 10 s before initiation of scanning. To assure data acquisition throughout the cardiac cycle at a given tomographic region, four level scans (two contiguous scanner targets) were obtained at 20 images/level (total acquisition time 1,152 ms/level). Thus, data from a complete cardiac cycle could be obtained at all heart rates >50 beats/min. Initial scanning was begun on the two most caudal target rings. After a 2 to 5 min interval the patient received another contrast injection, and the two more cephalad target rings were activated according to the preceding protocol. Arterial pressure was measured by the cuff method and heart rate was noted before and immediately after each contrast injection.

Data analysis. At each tomographic level evaluated, curves of left ventricular volume versus time were constructed throughout the cardiac cycle. This was accomplished by identifying the endocardial border using previously validated methods of edge detection for ultrafast computed tomography (17), calculating the area within a given tomographic slice (3.3 mm²/pixel), multiplying by the
slice thickness (8 mm at full width, half maximum) and noting the reference time (50 ms scan time plus 8 ms interscan delay) for that given frame. These data were transferred to a separate microcomputer and displayed as a left ventricular volume versus time plot at each tomographic level. An example of such a curve from the mid-ventricle of one patient is shown on Figure 1. Note that this curve resembles a global left ventricular volume curve as might be recorded from contrast or radionuclide angiography. Rapid systolic emptying and the three distinct phases of diastole (early rapid filling, diastasis and atrial contraction) are evident.

**Left ventricular volume versus time data were reviewed for each of the eight tomographic levels in each patient.** The ejection fraction from the most apical scans was 95% to 100% in more than half of the subjects. This is partly because, during normal contraction, the left ventricular apex thickened longitudinally (as well as transversely) and the endocardial surface, as viewed in an externally fixed tomographic format, disappeared from view. For this reason, inability to identify the frame that represented true end-systole at the most apical level made evaluation of time-dependent volumetric data quite difficult. To allow for uniformity of analysis from the same tomographic levels in all patients, subsequent data analysis was not performed in any patient at the endocardial apex.

During normal contraction the most basal portion of the heart descends, as has been reported previously by investigators using ventriculography (25) and fast computed tomography (26). Thus, although the left ventricular endocardium was continuous in the most basal scan at end-diastole, the mitral valve plane frequently was evident at end-systole, making the separation between the left atrium and the left ventricle only subjective at best. For uniformity of data analysis and to allow objective comparisons among patients, subsequent data analysis was performed at only six contiguous tomographic levels commencing (level 1) with the first level in the apical segments that had a volume/time curve with a distinct and identifiable end-systolic (smallest area) frame (18–23). Figure 2 schematically characterizes the anatomic position of each tomographic scan.

**Diastolic dynamics measurements (Fig. 3).** After identification of the frames from each tomographic level that represented the lowest volume per cardiac cycle (end-systole), a third-order polynomial curve (method of least squares) was fit to the data from end-systole through the first 300 to 450 ms of diastole (rapid filling phase and early diastasis). At least five sequential values of diastolic tomographic cavity volume and time were employed to determine the maximal rate of regional early diastolic filling occurs at the inflection point. CI = computed tomography.
the best fit regression curve for the data (range 5 to 8). The time from end-systole at which the second derivative of the regression expression was equal to zero determined the time at which the peak left ventricular filling rate occurred. This time was then applied to the first derivative (slope) of the regression expression to determine the absolute peak filling rate per tomographic level (cubic centimeters/second). Such an analysis, as applied to global volume information, has been used by other investigators when evaluating diastolic function from radionuclide angiography (3-6, 13).

This data analysis was repeated for each of the six distinct tomographic levels in each of the 11 patients (for all curve fits mean r = 0.96, range 0.92 < r < 1.0). Additionally, at each tomographic level the regional end-diastolic volume, end-systolic volume, stroke volume and ejection fraction were calculated. The percent of left ventricular diastolic filling volume achieved by the time of peak early diastolic filling (filling fraction) for each region was calculated employing the regression equation for that tomographic level.

Statistical analysis. Data are presented as mean values ± SEM. Analysis of data from all subjects between tomographic levels was performed with a one-way analysis of variance (ANOVA) with a Neuman-Keuls multivariate analysis for evaluation of significance between tomographic levels set at α = 0.05.

Validation of the technique. To validate the technique to quantitate ventricular filling using ultrafast computed tomography, scans were done in an additional seven normal subjects (aged 21 to 30 years) following standard list mode equilibrium (technetium-99m) radionuclide imaging (3,4,6,13). Data sets of global left ventricular filling curves were acquired at a framing rate of 32/s. The data from end-systole through the rapid filling phase were then fit to a third-order polynomial curve and references global peak filling rates determined (EDV/s). After the radionuclide examination, the volunteers had a rest ultrafast computed tomographic scan performed at six left ventricular levels during infusion of iodinated contrast medium (Iohexol, 0.35 ml/kg). Data were acquired throughout systole and during the initial phases of diastole. Time-dependent ultrafast computed tomographic volume information was summed across the six levels evaluated and a “global” left ventricular time-dependent volume curve generated. Calculations of absolute peak filling rate (PFR) referenced to end-diastolic volume (PFR/EDV or EFV/s) were then performed in the manner previously described with use of the summed volume (based on six ventricular levels) versus time data.

The mean results for peak ventricular filling rates from the radionuclide study in these normal subjects were 3.3 ± 0.17 EDV/s (range 2.6 to 4.1) and for the ultrafast computed tomography data in the same group, 3.0 ± 0.14 EDV/s (range 2.6 to 3.5, P = NS) (Fig. 4). The mean difference between the calculations made for each patient with each method was 0.32 EDV/s, where the results from the radionuclide technique slightly exceeded the results from the computed tomographic technique.

Results

Hemodynamics. Mean arterial pressure in the 11 normal subjects was 106 ± 2 mm Hg and mean heart rate 74 ± 3 beats/min immediately before scanning. Values for either of these variables immediately after scanning varied <10% from the values before scanning. Thus, the data from the two scan series required for the complete data set were assumed to represent the same ventricular loading conditions.

Mean global systolic and diastolic dynamics for the left ventricle. Mean left ventricular ejection fraction (based on the six levels examined in the 11 subjects) was 77 ± 2% (range 62 to 85%). The mean rate of peak early diastolic filling, as a linear average of data from the six tomographic levels, was 259 ± 17 ml/s (range 173 to 346 ml/s) whereas mean filling fraction was 39 ± 2% (range 32 to 44%). Mean time to peak filling from end-systole for the six ventricular levels examined was 145 ± 5 ms (range 121 to 167). Peak filling rate referenced to end-diastolic volume (EDV) was 3.78 ± 0.17 EDV/s (range 2.58 to 4.32). The value for mean peak filling rate across the ventricle referenced to stroke volume (SV) averaged 4.83 ± 0.20 SV/s (range 3.67 to 5.83).

Regional Diastolic Dynamics (Table 1)

Regional (tomographic) peak rate of early diastolic filling. Across tomographic levels, there was a significant difference in peak filling rate between level 1 (most apical) and the other five levels; however, there was no significant difference in peak filling rate between levels 3, 4, 5 or 6. The rate at level 2 was significantly different from that at level 6 but confirmed the general trend for absolute peak filling rate to increase from apex to base.
Table 1. Diastolic Filling Variables in 11 Normal Subjects Assessed by Ultrafast Computed Tomography

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 (Apex)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6 (Base)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFR (ml/s)</td>
<td>21.6 ± 2.3*</td>
<td>43.1 ± 3.4</td>
<td>53.7 ± 5.6</td>
<td>53.6 ± 5.8</td>
<td>55.9 ± 6.5</td>
<td>64.2 ± 5.6</td>
</tr>
<tr>
<td>PFR/EDV (s⁻¹)</td>
<td>4.5 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>4.2 ± 0.3</td>
<td>3.7 ± 0.2</td>
<td>3.3 ± 0.3†</td>
<td>3.3 ± 0.2†</td>
</tr>
<tr>
<td>PFR/SV (s⁻¹)</td>
<td>4.7 ± 0.3</td>
<td>5.2 ± 0.3</td>
<td>5.1 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>4.5 ± 0.4</td>
<td>4.7 ± 0.2</td>
</tr>
<tr>
<td>TPF (ms)</td>
<td>125 ± 10</td>
<td>145 ± 10</td>
<td>145 ± 10</td>
<td>156 ± 8</td>
<td>144 ± 13</td>
<td>136 ± 10</td>
</tr>
<tr>
<td>FF (%)</td>
<td>37 ± 2</td>
<td>40 ± 2</td>
<td>38 ± 2</td>
<td>39 ± 2</td>
<td>41 ± 2</td>
<td>37 ± 2</td>
</tr>
</tbody>
</table>

*p < 0.005 versus levels 2 through 6; †p < 0.05 versus levels 1, 2, and 3; data are expressed as mean values ± SEM. EDV = end-diastolic volume per tomographic level; FF = filling fraction as a percent of total filling (at time of peak filling) per tomographic level; PFR = peak filling rate per tomographic level; SV = stroke volume per tomographic level; TPF = time to peak filling (from end-systole) per tomographic level.

Regional filling fraction (Table 1). Filling fraction was determined from the regression equation at each level in each subject and is given as the mean of values from the 11 patients at each tomographic level examined. Filling fraction was remarkably uniform across the ventricle as a whole (p = NS).

Regional time to peak filling. Time to peak filling was determined as the time from end-systole to the time of maximal filling rate per tomographic level directly from the regression equation. The mean value for time to peak filling did not vary significantly across the tomographic regions examined (p = NS).

Regional (tomographic) peak filling rate/end-diastolic volume. Values of the regional (tomographic) peak rate of filling referenced to tomographic left ventricular end-diastolic volume are shown on Figure 5. This variable is equivalent to the variable EDV/s (end-diastolic volumes/s), commonly employed in radionuclide imaging to assess early diastolic filling (3,4,13,14). Statistically significant differences were seen between the three most apical levels (1, 2 and 3) compared with the more basal levels (5 and 6). The value for EDV/s at the most apical level examined was 120% of the average value across regions, whereas the value at the most basal section examined was only 87% of the average value across the regions analyzed.

Regional (tomographic) peak filling rate/stroke volume. Values of regional peak filling rate referenced to regional left ventricular stroke volume (per tomographic level) are shown on Figure 6. No statistically significant difference was apparent when all levels were considered as a whole (p = NS). This result is in contrast to the results using regional tomographic end-diastolic volume as a reference for peak filling rates.

Discussion

Pattern of normal regional early diastolic filling. This study constitutes the first detailed evaluation of the pattern of regional left ventricular early diastolic filling in normal subjects. The major observation is that left ventricular diastolic function is variable from apex to base in the normal human left ventricle, but this variability is highly dependent on the variable chosen for evaluation. An independent validation study, using time-dependent volume information summed across the six tomographic regions employed in our ultrafast computed tomographic analysis of regional diastolic filling, compares quantitatively with global radionuclide angiographic data, as a reference standard in the same subject.

Figure 5. Regional (tomographic) peak filling rate referenced to tomographic end-diastolic volume (EDV/s) in the 11 normal subjects at the six left ventricular levels evaluated. Levels 1 to 3 are statistically different from levels 5 and 6. There was no statistically significant difference between levels 3 through 6. Data are mean values ± SEM.

Figure 6. Regional (tomographic) peak filling rate normalized to tomographic stroke volume (SV/s) in the 11 normal subjects at the six levels evaluated. There is no statistical difference among levels. Data are mean values ± SEM.
This section will address three specific areas: technical considerations that relate to measuring left ventricular filling rates with ultrafast computed tomography, factors that may influence left ventricular diastolic filling in the normal human ventricle and, finally, clinical implications of this study.

Technical considerations related to the use of ultrafast computed tomography. The advantages of ultrafast computed tomography for evaluative left ventricular diastolic filling are manifold. In particular, because of the favorable spatial resolution, absolute values of regional and global variables such as stroke volume, ejection fraction, end-diastolic volume and end-systolic volume can be determined using previously validated methods for cardiac edge detection (17-20).

Temporal resolution. However, the temporal resolution of ultrafast computed tomography (17 frames/s) is substantially lower than that of most other techniques commonly used to assess peak diastolic filling rates (contrast ventriculography, echocardiography and radionuclide angiography). Nonetheless, three lines of evidence suggest that the framing rate of ultrafast computed tomography is sufficient to accurately define time-dependent volumetric data in patients at rest. First, Bove et al. (27) performed a cineangiographic evaluation (270 frames/s), where calculations of left ventricular time-dependent volume were made using Simpson’s rule. They found that framing rates as low as 10 frames/s were sufficient to adequately define left ventricular volumetric data on a time-dependent basis. Second, Bacharach et al. (28) evaluated peak left ventricular early diastolic filling rates in a group of patients with and without coronary artery disease and compared values of peak filling rate (EDV/s) at variable framing rates from 100/s to 20/s. Their results indicated that a framing rate of 25 frames/s was sufficient to evaluate peak early diastolic filling at rest. On further evaluation of their data, when a framing rate of 20/s was examined, the error between 20 and 25 frames/s was 5% to 10%. Therefore, the framing rate of 17 frames/s achievable with ultrafast computed tomography is probably sufficient to evaluate early left ventricular diastolic filling in patients at rest, but probably not during exercise (heart rate >90 to 100 beats/min).

Comparison with radionuclide angiography. Finally, support for the data on global estimates of peak filling rates is found in the separate group of seven normal subjects in the current study. When radionuclide and ultrafast computed tomographic data were directly compared, no statistical difference was found in calculations of peak filling rate referenced to end-diastolic volume, although estimates made by radionuclide angiography were 10% greater than similar calculations by computed tomography (Fig. 4). If the temporal resolution of ultrafast computed tomography was a major problem, one would expect that mean peak filling rates measured with this method would be significantly lower than those values calculated from routine radionuclide angiography, but this was not the case.

Cardiac motion during contraction and relaxation. Such motion is complex and occurs in several different planes. In addition to movement of the left ventricular endocardial surface toward an ill defined center within any given short-axis plane, the ventricle during systole tilts out of the initial reference plane, undergoes torsion and translation and displays distinct descent of the base parallel to the long axis. Because only total tomographic endocardial motion was evaluated and not segmental motion, the translation and rotation that occur within that plane should not affect the described measurements. However, the ventricular tilt and up and down motion may contribute artifactual to our measurements because these occur in a plane not parallel to the short-axis (transverse) imaging plane. Movement of the base has been observed during angiography (25) and during studies using computed tomography (Dynamic Spatial Reconstructor) (26), whereas the position of the epicardial apex remains relatively fixed during the cardiac cycle. However, thickening of the apical myocardium in the longitudinal direction gives the “appearance” of endocardial motion in and out of the imaging plane at the most apical segment. To partially eliminate these observations as sources of measurement errors from the final analysis, the most basal and most apical tomographic images from the left ventricle were excluded. However, elimination of these two levels does not appear to significantly affect global estimates of diastolic filling (Fig. 4). Although complex cardiac movements may contribute artifactual information to the remaining data set, it is important to note that all planar and tomographic imaging techniques share this potential source of artifactual information because contraction is a three-dimensional event. This problem can only be fully eliminated by a very sophisticated and detailed three-dimensional reconstruction that cannot be performed at present with the current ultrafast computed tomographic format.

Despite the potential technical problems related to temporal resolution and complex cardiac motion during contraction and relaxation, it appears that ultrafast computed tomography can be used to assess peak filling rates of the human left ventricle at rest with reasonable accuracy as well as define the patterns of left ventricular diastolic filling from the apex to the base.

Factors that contribute to diastolic function. Apex to base evaluation of systolic function (ejection fraction, stroke volume) has indicated that it is nonuniform across the left ventricle as a whole (20). Left ventricular diastolic filling is an active process influenced by many physiological factors that may include diastolic suction (29,30), alterations of global contractile state (31), external forces (right ventricular pressure, pericardial pressure) (32,33), end-diastolic loading conditions (34), afterload (35) and myocardial viscoelastic properties (36,37). Because these factors may not act in a
homogeneous fashion on the left ventricle, it is not unreasonable to expect that absolute rates of regional left ventricular diastolic filling would be variable from apex to base. Currently, it is not known if other factors that alter global systolic and diastolic function (e.g., hypertrophy [15], ischemic disease [3,4,14], aging [38]) exert their influences in a uniform or nonuniform fashion.

**Variables used to describe diastolic filling.** Two variables (absolute peak filling rate alone or referenced to end-diastolic volume) demonstrated apex to base nonuniformity whereas three other commonly used variables (filling fraction, time to peak filling and peak filling rate referenced to stroke volume) demonstrated highly uniform patterns from apex to base. From these data it is evident that the variables chosen for analysis have a major impact on whether regional diastolic filling is perceived as uniform or nonuniform. A comparison of absolute peak filling rate between individual ventricles may not allow for the ready detection of distinct pathologic states for the left ventricle. However, reference of the absolute peak filling rate to end-diastolic volume potentially allows for comparisons of filling variables between ventricles of different sizes (39). This does not mean that reference to stroke volume per tomographic level would also allow a ready comparison between ventricles of different sizes and shapes. A recent study by Udelson et al. (40) suggests that global information regarding both end-diastolic and end-systolic volume per second may be useful descriptors of diastolic function where changes in these variables parallel each other in the presence of cardiac disease.

It is reasonable to assume that regional diastolic filling in the normal subject is mandated by the time available for the filling to occur (diastolic filling period) and the magnitude of the filling required in preparation for subsequent systolic emptying. The absolute rate of filling and the final end point (end-diastolic volume), independent of the point of origin (end-systolic volume), may thus be poor variables to employ when considering conditions that may pathologically alter diastolic function. As such, the required amount of systolic emptying (stroke volume) should perhaps be more closely connected to the rate of diastolic filling. The data presented here confirm that regional diastolic filling mechanics are uniform across the normal human left ventricle with respect to variables that relate to regional stroke volume (SV/s., filling fraction) and the time at which peak filling occurs.

**Clinical implications.** Any description of regional diastolic filling in patients with ischemic disease or any other definable myocardial process should take into consideration the patterns of regional filling such as those described herein using ultrafast computed tomography in normal subjects. It is clear from the previous discussion that the definition of uniformity or nonuniformity in regional left ventricular early diastolic filling depends significantly on the variables chosen for evaluation. As clinicians become more interested in quantitation of regional left ventricular function, the ability to precisely define the patterns of left ventricular diastolic filling becomes more important. From the data presented, patterns of regional diastolic function must be intimately related to patterns of systolic function and ventricular size within that same region. Asynchronous regional diastolic function in the presence of regional abnormalities of systolic function has been reported (41,42). A proper method to evaluate diastolic filling characteristics of the human left ventricle requires that both global and regional patterns be evaluated in the same fashion as routine evaluation of systolic function and ventricular size.

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**References**


