Evaluation of Right Ventricular Early Diastolic Filling by Cine Nuclear Magnetic Resonance Imaging in Patients With Hypertrophic Cardiomyopathy

JUN-ICHI SUZUKI, MD,* JINN-MING CHANG, MD, GARY R. CAPUTO, MD, CHARLES B. HIGGINS, MD, FACC
San Francisco, California

Numerous studies have established abnormalities in systolic and diastolic function of the left ventricle in hypertrophic cardiomyopathy. A consistent feature of this disease is reduced diastolic function of the left ventricle, but little information is available regarding right ventricular function in this disease. Cine nuclear magnetic resonance (NMR) imaging has been found to be effective for measuring right ventricular volumes and therefore was used to assess early diastolic filling of the right ventricle in patients with hypertrophic cardiomyopathy.

Right ventricular time-volume curves were obtained from cine NMR images in 10 patients with hypertrophic cardiomyopathy and 8 normal subjects. Right ventricular volume was calculated with use of Simpson's algorithm at approximately 18 phases of the cardiac cycle and, from the curve, peak filling rate and filling fraction during the first third of diastole were determined.

In patients with hypertrophic cardiomyopathy, peak filling rate tended to be less (176 ± 46 vs. 305 ± 50 ml/s, \(p < 0.01\)) and filling fraction decreased (39.5 ± 13.8 vs. 74.5 ± 13.3%, \(p < 0.01\)) in comparison with values in normal subjects.

Thus, analysis of right ventricular time-volume curves obtained by using cine NMR imaging demonstrated diastolic dysfunction of the right ventricle in hypertrophic cardiomyopathy.

From the Department of Radiology, University of California, San Francisco, California. *Present address: The Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan.

Manuscript received June 11, 1990; revised manuscript received September 11, 1990, accepted March 15, 1991.

Address for reprints: Charles B. Higgins, MD, Department of Radiology, C309, Box 0628, University of California, San Francisco, California 94143.

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Methods

Study patients. A right ventricular time-volume curve was obtained in 18 subjects with use of cine nuclear magnetic resonance (NMR) imaging. The subjects were 10 patients with hypertrophic cardiomyopathy (hypertrophic cardiomyopathy group: mean age 55.4 ± 20.9 years, heart rate: 62.1 ± 10.6 beats/min) and 8 asymptomatic volunteers (normal group: mean age 30.4 ± 4.8 years, heart rate 62.4 ± 4.3 beats/min). No history of congenital heart disease, valvular heart disease, ischemic heart disease or cardiomyopathy was confirmed and NMR findings of the left ventricle were normal in all asymptomatic volunteers. All patients in the hypertrophic cardiomyopathy group had echocardiographically documented asymmetric septal hypertrophy with septal thickness ≥16 mm. The maximal end-diastolic wall thickness of the left ventricle measured with NMR imaging was 24.3 ± 6.7 mm in the hypertrophic cardiomyopathy group.

All subjects gave informed consent and the research and consent form was approved by the Institutional Committee on Human Research.

Cine NMR imaging. The electrocardiographically referenced gradient refocused technique was used with a 1.5 T superconducting magnet (Signa, General Electric). The im-
aging variables were echo time of 5 to 17 ms, pulse repetition
time of 20 to 31 ms with effective repetition time at each level
of 40 to 62 ms and flip angle of 30°. The heart was encom­
passed with use of a double oblique slice selective gradient
with acquisition of 12 contiguous slices with 10 mm slice
thickness in the cardiac short-axis plane. The number of time
frames per cardiac cycle acquired at each level was 18.4 ±
5.0 frames (average pulse repetition time 55.1 ± 10.2 ms).
There was no significant difference in the time frames per
cardiac cycle for patients with hypertrophic cardiomyopathy
(19.1 ± 5.4 frames, average pulse repetition time 54.0 ±
10.7 ms) compared with normal subjects (17.5
± 4.5 frames,
average pulse repetition time 56.4 ± 10.2 ms). The total time
needed to acquire a study was 60 to 80 min.

**Reconstruction of right ventricular time-volume curve and
the first derivative of the curve.** A Simpson’s rule approach
was applied to cine NMR images in short-axis cross-
sectional planes. The areas of the right ventricular chamber
were measured by planimetry (area calculation algorithm in
the imager software) of each slice at each phase of the
cardiac cycle. The volume was calculated by summing the
areas in the adjacent slices encompassing the entire right
ventricle (average 6.3 ± 1.0 slices) and multiplying by the
slice thickness.

To standardize window width and level setting for tracing endocardial and epicardial borders, representative signal
intensities of the ventricular blood pools, myocardium, lung
and intrapericardial space were measured for each image.
The intensity of the myocardium was set as the window level

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**Figure 1.** Three anatomic levels (A, Apical level; B, Midventricular
level; C, Basal level) of cine nuclear magnetic resonance images
obtained at end-diastole from a patient with mild hypertrophic
cardiomyopathy. D, This image was produced at the window
settings used to trace the endocardial margins (midventricular level).
In C, the right atrium (RA), the right ventricular outflow tract
demonstrated by white outline and the pulmonary valve (PV) can
be seen on this basal image.
(midpoint of the window). The intensity difference between the blood pool and the myocardium multiplied by 1.5 was defined as the window width for tracing of the endocardium (Fig. 1). The difference of intensity between the myocardium and the structures immediately external to the myocardium multiplied by 1.5 was used for tracing the epicardium.

The heart was encompassed with 12 anatomic levels in two or three imaging periods consisting of 6 or 4 levels, respectively. The heart rate remained relatively constant during imaging but varied as much as 6 beats/min in some subjects. Variations in heart rate in some patients caused the number of frames per cardiac cycle to vary by 1 among acquisitions in the same patient. To compensate for this variation among anatomic levels, the time frames were adjusted by simple linear interpolation. This time compensation technique was used in 9 of the 18 subjects; in the remaining subjects an equal number of frames was used at the various anatomic levels.

The first derivative curve was obtained by calculating volume differences of adjacent two points on the right ventricular volume curve divided by the average time between points (the time between points was equal to effective pulse repetition time).

Ventricular volumes and mass. At the base of the ventricles, the right ventricle was distinguished from the right atrium because the contour of the right atrium increased during systole. Likewise, only myocardium that thickened in systole, indicating that it was left ventricular myocardium, was included in left ventricular mass measurements. These judgments were made by viewing the cine loops. End-diastolic and end-systolic volumes of the right ventricle were obtained from the right ventricular time-volume curve. In the current study, 32 ms after the R wave (the first cardiac frame) was used for end-diastolic measurements and the timing of end-systole was defined as the minimal point on the right ventricular time-volume curve. Left ventricular end-diastolic and end-systolic volumes were reconstructed by using the sets of images in common cardiac phase that gave maximal and minimal volumes, respectively. Left ventricular mass was reconstructed with Simpson's algorithm; for this measurement the end-systolic images were used. Left ventricular mass included the ventricular septum in the measurement. A specific gravity of 1.05 (g/ml) was used for calculation of ventricular mass.

Indexes of diastolic function of the right ventricle. The following variables were measured from the right ventricular time-volume curve and the first derivative of the curve: 1) peak filling rate (ml/s): the maximal rate of increase of right ventricular volume; 2) the time to peak filling rate (s): the time interval between end-systole and the time point of the peak filling rate; and 3) volume increase (ml) and filling fraction (%) during the first third of diastole: absolute value and percent (normalized by right ventricular stroke volume) of the increase of right ventricular volume during the first third of diastole.

The time point of the peak filling rate was defined as the maximal point on the curve of the first derivative. For the statistical analyses of the indexes of peak filling rate and time to peak filling rate, we excluded those patients with hypertrophic cardiomyopathy whose peak filling rate occurred in late diastole during the atrial contraction period (last 0.25 s of the diastolic period), because in these patients the value of peak filling rate does not represent properties of the early diastolic filling and time to peak filling rate does not parallel the properties.

Intraobserver and interobserver variabilities for measurement of area of the right ventricular cavity. To evaluate intraobserver and interobserver variabilities for this measurement, the 262 areas of the cavity on 262 frames at 16 levels from 16 cases were measured twice by the first observer and once by a second observer. Intraobserver and interobserver variabilities were expressed as the absolute difference divided by the mean of the two paired measurements.

Statistical analysis. All values are expressed as mean values ± SD. Differences between the two groups were tested by the unpaired t test. A significant difference was indicated by a p value < 0.05.

Results

Right and left ventricular volumes. The stroke volume of the right and left ventricles was 56.8 ± 8.5 and 55.9 ± 10.8 ml, respectively; these values included data from all subjects of the current study except for one patient with hypertrophic cardiomyopathy who had moderate mitral regurgitation. Absolute difference of the two stroke volumes divided by the average of these two stroke volumes was 8.1 ± 5.8% (hypertrophic cardiomyopathy group 8.8 ± 6.8%, normal group 7.4 ± 4.8%). Right ventricular end-diastolic volume of the hypertrophic cardiomyopathy group (89.6 ± 18.1 ml) was smaller than that of the normal group (119.2 ± 15.4 ml) (p < 0.01); the right ventricular end-systolic volume of the hypertrophic cardiomyopathy group (36.1 ± 11.7 ml) was smaller than that of the normal group (59.3 ± 14.0 ml) (p < 0.01). The ejection fraction of the right ventricle of the hypertrophic cardiomyopathy group (60.1 ± 6.3%) was greater than that of the normal group (50.8 ± 6.9%) (p < 0.05).

Intraobserver and interobserver variabilities for measurement of area of the right ventricular cavity. Intraobserver variability was 4.8 ± 6.0% and interobserver variability was 7.3 ± 7.9%.

Indexes of right ventricular diastolic function (Table 1). Examples of the right ventricular time-volume curve and the first derivative of the curve in a patient with hypertrophic cardiomyopathy and a normal subject are shown in Figures 2 and 3, respectively.

Absolute volume increase (hypertrophic cardiomyopathy group 21.2 ± 8.4 ml, normal group 44.5 ± 8.5 ml; p < 0.01) and filling fraction (hypertrophic cardiomyopathy group 39.5 ± 13.8%, normal group 74.5 ± 13.3%; p < 0.01) during
Table 1. Indexes of Right Ventricular Early Diastolic Filling in 10 Patients With Hypertrophic Cardiomyopathy and 8 Normal Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>RVFPR* (ml/s)</th>
<th>RVFPR/RVEDV* (l/s)</th>
<th>RVTPFR* (s)</th>
<th>RVDV (ml)</th>
<th>RVFF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>176 ± 46†</td>
<td>2.1 ± 0.5</td>
<td>0.22 ± 0.14</td>
<td>21.2 ± 8.4†</td>
<td>39.5 ± 13.8†</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>305 ± 50</td>
<td>2.6 ± 0.5</td>
<td>0.11 ± 0.07</td>
<td>44.5 ± 8.5</td>
<td>74.5 ± 13.3</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
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</tr>
</tbody>
</table>

Values are expressed as mean values ± SD. †For these comparisons five patients with hypertrophic cardiomyopathy whose peak filling rate occurred in late diastole were excluded. In these patients peak filling rate was thought to be related to atrial contraction. p < 0.01. HCM = hypertrophic cardiomyopathy; RVDV = absolute right ventricular volume increase during the first third of diastole; RVEDV = right ventricular end-diastolic volume; RVFF = filling fraction of the right ventricle; RVFPR = peak filling rate of the right ventricle; RVTPFR = time to peak filling rate of the right ventricle.

the first third of diastole were lower in the hypertrophic cardiomyopathy group than in the normal group.

Five patients with hypertrophic cardiomyopathy whose peak filling rate occurred in late diastole (the last 0.17 ± 0.06 s of the diastolic period) were excluded for analyses of peak filling rate and time to peak filling rate. Absolute volume increase (16.2 ± 6.3 ml) and filling fraction (29.4 ± 10.1%) were severely decreased in these five excluded patients. Peak filling rate (hypertrophic cardiomyopathy group 176 ± 46 ml/s, normal group 305 ± 50 ml/s; p < 0.01) was lower in the hypertrophic cardiomyopathy group. Although there was no significant difference between the two groups, time to peak filling rate (hypertrophic cardiomyopathy group 0.22 ± 0.14 s, normal group 0.11 ± 0.07 s; p = 0.09) tended to be prolonged. Peak filling rate divided by right ventricular end-diastolic volume (hypertrophic cardiomyopathy group 2.1 ± 0.5 l/s; normal group 2.6 ± 0.5 l/s, p = 0.09) tended to be decreased in the hypertrophic cardiomyopathy group.

Relation between indexes of right ventricular early diastolic filling and left ventricular mass. There was an inverse correlation between right ventricular filling fraction and left ventricular mass index (r = 0.78, p < 0.01). However, there was no significant correlation between other indexes of right

Figure 2. Time-volume curve of the right ventricle (upper panel) and its first derivative curve (lower panel) from a patient with hypertrophic cardiomyopathy. dV = absolute increase of right ventricular volume during the first third of diastole; ES = end-systole; FF = filling fraction (calculated as dV/RSV); 1/3 Diastole = the first third of diastole. Because the maximal rate of volume increase can be seen in the atrial contraction period, this case was excluded for statistical analyses of peak filling rate and time to peak filling rate.

Figure 3. Time-volume curve of the right ventricle (upper panel) and its first derivative curve (lower panel) from a normal subject. PFR = peak filling rate; TPFR = time to peak filling rate. Other abbreviations as in Figure 2.
ventricular early diastolic filling and left ventricular mass or mass index in the hypertrophic cardiomyopathy group.

Discussion

Time-volume curves of the right ventricle. Time-volume, time-dimension and time-activity curves of the left ventricle obtained with contrast left ventriculography (2), M-mode echocardiography (3–5) and radionuclide angiography (6,11–13) have been used to estimate early diastolic filling of the left ventricle. The complicated shape of the right ventricle makes it difficult to apply a simple geometric model to obtain right ventricular volumes from either single plane or biplane cineangiography. It is also difficult to obtain images of the entire right ventricle with use of two-dimensional echocardiography. Although the time-activity curve of the right ventricle obtained with radionuclide methods has been available, detailed analysis of the time-activity curve has been limited by the contribution of the right atrium to the ventricular activity curve due to right atrial-right ventricular overlap. Thus, it has not been feasible to obtain an accurate time-volume curve of the right ventricle with traditional methods.

To obtain the time-volume curve of the right ventricle with application of Simpson’s algorithm, a set of cross-sectional images that encompass the entire right ventricle with clear endocardial margins is required at multiple phases in the cardiac cycle. Nuclear magnetic resonance (NMR) imaging is an effective method to obtain such images of the right ventricle (7,14) and the capability of cine NMR imaging for measuring right (9) and left (10) ventricular volumes has been shown. Therefore, cine NMR imaging was used to assess early diastolic filling of the right ventricle in the current study. The normal values for filling indexes of the left ventricle were known; that is, the left ventricular peak filling rate is <0.18 s (15). In the current study the indexes of left ventricular early diastolic filling in the normal group were evaluated with the same method that was applied to the right ventricle (Table 2). The normal values for filling indexes of the left ventricle obtained with cine NMR imaging in the current study were similar to those for the left ventricle reported previously with use of radionuclide methods. This observation suggests that the techniques used for monitoring right ventricular time-volume curves with this method are reasonable. However, the clinical applicability of this method will require automation edge definition for volume measurement because manual analysis of imaging data now requires several hours per study.

Right ventricular dysfunction in hypertrophic cardiomyopathy. In hypertrophic cardiomyopathy, an intrinsic functional disorder is impaired diastolic function of the left ventricle. Such dysfunction has been shown with cardiac catheterization (1,2), echocardiography (3–5) and radionuclide angiography (6). Anatomic involvement of the right ventricle in hypertrophic cardiomyopathy is known and hypertrophy of the free wall of the right ventricle has been demonstrated (7,8). These observations raise the question of functional abnormality of the right ventricle. On the basis of the findings of the time-volume curve obtained with cine NMR imaging in the current study, both impaired early diastolic filling and elevated systolic function of the right ventricle were demonstrated in patients with hypertrophic cardiomyopathy.

Variables that can influence early diastolic filling. Previous studies using conventional methods have shown that the dynamics of diastolic filling of the left ventricle are influenced not only by left ventricular diastolic function, but also by physiologic variables such as heart rate (16), left ventricular volume (13), left ventricular ejection fraction or inotropism (17) and age (18–20). Increased heart rate augments the rapid filling rate and reduces the filling fraction of the left ventricle. Decreased left ventricular end-diastolic

Table 2. Indexes of Left Ventricular Early Diastolic Filling in the Eight Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>LVFPR</th>
<th>LVFPR/LVEDV</th>
<th>LVTPFR</th>
<th>LVdV</th>
<th>LVFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ml/s)</td>
<td>(l/s)</td>
<td>(%)</td>
<td>(s)</td>
<td>(ml)</td>
<td>(%)</td>
</tr>
<tr>
<td>321 ± 50</td>
<td>3.4 ± 0.8</td>
<td>0.15 ± 0.03</td>
<td>39.9 ± 5.6</td>
<td>65.8 ± 9.4</td>
<td></td>
</tr>
</tbody>
</table>

The same methods that were used for the right ventricle were applied to obtain the indexes of left ventricular early diastolic filling in eight normal subjects. LVdV = absolute volume increase of the left ventricle during the first third of the diastole; LVEDV = left ventricular end-diastolic volume; LVFF = left ventricular filling fraction; LVFPR = peak filling rate of the left ventricle; LVTPFR = time to peak filling rate of the left ventricle.

Table 3. Comparison Between the Two Patient Groups of Variables That Can Influence Right Ventricular Early Diastolic Filling

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>HR (beats/min)</th>
<th>RVEDV (ml)</th>
<th>RVESV (ml)</th>
<th>RVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>55.4 ± 20.9*</td>
<td>62.1 ± 10.6</td>
<td>89.6 ± 18.1*</td>
<td>36.1 ± 11.7*</td>
<td>60.1 ± 6.3*</td>
</tr>
<tr>
<td>Normal</td>
<td>30.4 ± 4.8</td>
<td>62.4 ± 4.3</td>
<td>119.2 ± 15.4</td>
<td>59.3 ± 14.0</td>
<td>50.8 ± 6.9</td>
</tr>
</tbody>
</table>

*p < 0.01, tP < 0.05. Values are expressed as mean values ± SD. HR = heart rate; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; other abbreviations as in Table 1.
filling pattern of the left ventricle. Aging is associated with differences in these variables between the two groups would be expected to augment the filling function in the hypertrophic cardiomyopathy group. Right ventricular diastolic function was impaired, as was also observed in the older patients. Thus, alteration of the pattern of early diastolic filling in the hypertrophic cardiomyopathy group strongly suggests the existence of diastolic dysfunction of the right ventricle in hypertrophic cardiomyopathy, which is not entirely related to age.

Relation between diastolic function and the extent of hypertrophy. The possibility of a causal relation between indexes of the early diastolic filling of the left ventricle and the extent of hypertrophy of this chamber is still controversial (21,22). Left atrial pressure and left ventricular relaxation are important determinants of early diastolic filling (23). Accordingly, in a severely hypertrophied heart, the indexes could be paradoxically normalized because of elevated left atrial pressure (22). In the present study indexes of early diastolic filling of the right ventricle did not correlate with either left ventricular mass or left ventricular mass index except for a weak relation between left ventricular mass index and right ventricular filling fraction. The relation of filling indexes of the right ventricle to right ventricular mass was not defined because of concern regarding accuracy of the measurement for the thin free wall of the right ventricle in relation to the spatial resolution of 1.3 × 2.6 mm for cine NMR imaging.

Limitations. To encompass the entire right ventricle during a reasonable examination time, pulse acquisitions were performed alternately at two anatomic levels. This caused the effective repetition time for each slice to be 40 to 62 ms (average 55.1 ± 10.2). This temporal resolution is less than optimal for detailed analysis of the time-volume curve. However, the time resolution of the current study was adequate to identify a difference in the diastolic function of the right ventricle between the patients with hypertrophic cardiomyopathy and normal subjects.

Conclusions. Cine nuclear magnetic resonance imaging provided time-volume curves of the right ventricle. With use of this curve and its first derivative curve, impairment of diastolic function of the right ventricle in hypertrophic cardiomyopathy was demonstrated.

We thank Margaret O’Sullivan for her help.

Table 4. Indexes of Right Ventricular Early Diastolic Filling in Three Young Patients With Hypertrophic Cardiomyopathy and Eight Normal Subjects

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>RVPFR (ml/s)</th>
<th>RVTFPR (s)</th>
<th>RVFF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young HCM</td>
<td>26.7 ± 1.5</td>
<td>190 ± 28*</td>
<td>0.37 ± 0.06†</td>
</tr>
<tr>
<td>(n = 3)</td>
<td>(n = 2)</td>
<td>(n = 2)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td>Normal</td>
<td>30.4 ± 4.8</td>
<td>305 ± 50</td>
<td>0.11 ± 0.07</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01. Values are expressed as mean values ± SD. One young patient with hypertrophic cardiomyopathy whose peak filling rate occurred in late diastole was excluded for analyses of right ventricular peak filling rate and time to peak filling rate. Abbreviations as in Table 1.

References