INHOMOGENEOUS CONTRIBUTION OF LATE DIASTOLIC FILLING TO FILLING VOLUME IN PATIENTS WITH ISOLATED DISEASE OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY: ASSESSMENT WITH RADIONUCLIDE VENTRICULOGRAPHY

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Contributions of late diastolic filling (slow filling and atrial systolic phases) to total filling volume in both global and regional left ventricle were analyzed using radionuclide techniques in 21 patients with isolated left anterior descending coronary artery disease without previous myocardial infarction. A computer program subdivided the image of the left ventricle into four regions at a geometric center of the area. The time-activity and its first-derivative curves of the global and regional left ventricles were computed. In the global left ventricle, the percent contributions of late diastolic filling to total filling volume were significantly increased in patients with one-vessel disease than in control subjects (20 ± 5%, 28 ± 4%; p < 0.001). In the regional left ventricle, in patients with one-vessel disease, the percent contributions of late diastolic filling to total filling volume were significantly increased in the septal (25 ± 5%, 34 ± 8%; p < 0.001) and in the apical regions (21 ± 4%, 28 ± 4%; p < 0.001) which were perfused by stenosed vessel. In contrast, there were no significant differences in this value between the two groups in the normally perfused lateral region (22 ± 6%, 25 ± 5%; p = NS). These results indicate that the late diastolic filling makes a larger contribution to the left ventricular filling in the affected regions than in the normally perfused regions, and that the increased late diastolic filling in the affected regions are the cause for the increased late diastolic filling in the global left ventricle in patients with one-vessel disease.

Many patients with coronary artery disease have abnormal left ventricular diastolic filling, manifested by the diminished contribution of rapid diastolic filling and the increased dependence on atrial systole for left ventricular filling volume. However, little is known regarding the effect of the regional filling in the left ventricular cavity on the global left ventricular filling in these patients. Recent developments of computer technology permit the assessment of regional left ventricular function with the use of a scintillation camera interfaced to a computer system. We used this computer-assisted technique to quantitatively assess regional left ventricular function based on change of count

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rates, a variable which is directly proportional to changes in left ventricular volume. In this study, we used left ventricular time-activity curves obtained by radionuclide ventriculography to quantitate the contributions of late diastolic filling to left ventricular filling volume in patients with well-defined single-vessel disease in regions of the left ventricle as well as in the global left ventricle.

MATERIALS AND METHODS

Patient Population

The study group consisted of 35 patients (26 male and 9 female) referred to the Yamaguchi University Hospital between 1981 and 1983. All patients underwent electrocardiographically gated radionuclide ventriculography.

They were classified as follows: Group 1 consisted of 14 control subjects (8 male and 6 female, age range 20 to 64 years); Group 2 consisted of 21 patients with single-vessel disease of the left anterior descending coronary artery and angina pectoris (18 male and 3 female, age range 33 to 66 years). Each of the patients in group 1 underwent cardiac catheterization for the evaluation of atypical chest pain which did not always occur on effort or at rest and had a normal left ventriculogram and coronary arteriogram and normal values for hemodynamic variables at rest and during a supine bicycle exercise test or ergonovine maleate test. Physical examination (including determination of blood pressure), ECG, chest radiography, echocardiography, and stress myocardial scintigraphy with thallium-201 showed no abnormalities. All patients in group 2 underwent cardiac catheterization and had severe organic stenosis (>75% luminal diameter) of only the proximal left anterior descending branch. In all patients in group 2, the tracer uptake defects seen on the stress myocardial images obtained with thallium-201 were in the anteroapical or/and septal left ventricular wall and there were no defects in other areas. In five patients in group 2, resting electrocardiograms showed horizontal or sagging ST depression in left precordial leads, but the other patients in group 2 showed normal electrocardiographic findings. None of the patients had a history or electrocardiographic or ventriculographic evidence of previous myocardial infarction. Patients with additional coronary artery lesions, congenital heart disease, hypertensive heart disease, arrhythmia, valvular heart disease, or cardiomyopathy were excluded from the study. Patients with angina at rest or unstable chest pain were also excluded. Radionuclide study was performed at least 72 hours after cessation of calcium antagonists or beta-blockers and at least 12 hours after cessation of any nitrates.

The test was performed within 10 days before or after the cardiac catheterization. All patients of groups 1 and 2 were in normal sinus rhythm and they had no conduction disturbances. The radionuclide studies were preceded by resting myocardial scintigraphic studies with thallium-201 in all patients and subjects and the tracer uptake defects were not seen on the resting images from any of the 35. Patients who had a heart rate >85 beats/min were excluded from the study since the rapid diastolic filling and the atrial systolic portions of the time-activity curves were not clearly separated by a diastasis interval (or slow filling phase).

Gated Radionuclide Ventriculography

Multigated equilibrium blood pool imaging was performed with a conventional gamma camera (PHO/GAMMA LFOV, Searle Inc., Des Plaines, IL) equipped with a high-resolution all-purpose parallel-hole collimator. The technique used has been described in detail elsewhere. Briefly, all patients were given 15 to 20 mCi iv 99mTc-labeled human serum albumin. After the radionuclide had equilibrated with the intravascular space (about 10 min), the camera was positioned in the modified left anterior oblique projection (15 degrees caudal tilt). In all studies, low-count (500000 counts) scintigrams were acquired with a digital computer (Scintview, Searle Inc.) until the camera obliquity showing the greatest separation of the right and left ventricles was found (typically a 40 to 60 degree projection).

Then, counts were acquired during 600 beats in a multiple-gated mode (framing rate up to 31 frames/cardiac cycle) on a magnetic disc with a digital computer (SCINTIPAC-1200, Shimadzu Seisakusho, Kyoto, Japan). Data were collected for 600 beats in all studies. Those photoevents falling within a 20% window centered on the photopeak of technetium-99m were recorded.

After data acquisition, a summed-beats curve in which the number of summed beats in each frame was calculated explicitly, was constructed and the average cardiac cycle length was defined as the interval between the first frame and the frame that summed approximately 300 beats on
this curve (the last frame). To exclude the patients with extrasystole or wide spontaneous variation in sinus cycle length, only those who satisfied the following two conditions were included in this study: (1) 600 beats were summed explicitly in the frames before the terminal 10% portion of the average cardiac cycle length, (2) summed beats were abruptly decreased to zero near the last frame. The last three or four frames, which were undersampled due to artifacts produced by small changes in the R-R interval, were corrected according to the following equation. Corrected counts = Actual counts x 600 beats/actual summed beats.

The original multiple-gated mode data were collected on a magnetic disc with a computer with a 64 x 64 matrix. The $n^{th}$ frame included those counts falling in a 30 to 40 msec window ending $n \times 30$ to 40 msec from any R wave on the electrocardiogram.

Each 30 to 40 msec frame contained more than 30,000 counts within the left ventricular end-diastolic perimeter in patients with normal heart sizes. To improve visualization of the left ventricular perimeter, a 50% threshold was imposed on each frame — that is, matrix cells containing fewer than 50% of the maximum cell counts in the image were set equal to zero. This enhanced first image, which corresponded to the first 30 to 40 msec frame immediately after the R wave, was defined as the end-diastolic frame. A left ventricular longitudinal axis connecting the midpoint of the base and apex was rotated parallel to the y coordinate of the digital matrix and all hearts were oriented vertically on the end-diastolic images. The end-systolic frame was defined as the frame with the minimum counts within the end-diastolic perimeter of the left ventricle. Crescent-shaped global and regional background regions of interest were traced manually with an electronic cursor along the lateral, apical, and septal portions adjacent to and inside the left ventricular end-diastolic perimeter applied to the end-systolic frame, specifically avoiding regions of high-count activity. A computer program determined a geometric center of the area of the end-diastolic perimeter of the left ventricle and subdivided it into four regions (basal, septal, apical, and lateral), with two intersecting lines at an angle of 45 degrees to the longitudinal axis of the left ventricle at the geometric center of the area. The background correction for the four regions (septal, apical, and lateral regions and global left ventricle) was estimated with an average count per cell in each of the four background regions of interest obtained in the end-systolic frame.

Background-corrected global and regional time-activity curves were generated from the global left ventricle and each of three regions (septal, apical, and lateral) after three-point temporal smoothing using a fixed region of interest method. First-derivative curves (dV/dt) of these time-activity curves (V) were computed for the entire cycle in the septal, apical, and lateral regions and the global left ventricle according to the method described previously. Since the basal region of the left ventricle tended to overlie the regions of the mitral and aortic valves, aorta, left atrium, and great vessels, this region was excluded from study.

The following indices were obtained from the time-activity and first-derivative curves in the global left ventricle and in each of the three regions (septal, apical, and lateral) (Fig. 1). (1) Ejection fraction (%) = 100 x (EDV - ESV) / (EDV - BG), where EDV, ESV, and BG are end-diastolic, end-systolic, and background counts, respectively. (2) Time to end-systole (msec) = the time interval between the electrocardiographic R wave and the frame with minimum counts at which the dV/dt value is zero. (3) Rapid filling phase/diastolic time = rapid filling phase normalized to diastolic time (R-R interval - global time to end-systole) since heart rate or diastolic time affects the measurement of diastolic variables. Rapid filling phase was
defined as the time interval between the global end-systole and the point of the termination of the rapid filling phase at which the filling rate (dV/dt) had decreased to 50% of its peak positive value on the time-activity curves\(^8\) (Fig. 1). (4) Percent contribution of late diastolic filling to total filling volume (%) = percentage of filling volume during slow filling and atrial systolic phases to the total filling volume. The filling volume during the late diastolic filling phase was obtained by subtracting the filling volume during the rapid filling phase from the total filling volume, since the late diastolic phase of time-activity curves constructed with forward-gating radionuclide ventriculography was unreliable.

### TABLE I CLINICAL AND HEMODYNAMIC DATA

<table>
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<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
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<tr>
<td>Age (years)</td>
<td>50 ± 13</td>
<td>54 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 8</td>
<td>67 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.61 ± 0.12</td>
<td>1.62 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>125 ± 20</td>
<td>129 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>49 ± 9</td>
<td>51 ± 18</td>
<td>NS</td>
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<tr>
<td>Stroke volume (ml)</td>
<td>74 ± 17</td>
<td>78 ± 16</td>
<td>NS</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>61 ± 4</td>
<td>62 ± 7</td>
<td>NS</td>
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<tr>
<td>End-systolic pressure (mmHg)</td>
<td>133 ± 15</td>
<td>145 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic pressure (mmHg)</td>
<td>10 ± 4</td>
<td>11 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean aortic pressure (mmHg)</td>
<td>102 ± 10</td>
<td>105 ± 10</td>
<td>NS</td>
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Values are mean ± SD. Group 1 = control subjects; Group 2 = patients with single-vessel disease.

### TABLE II RADIONUCLIDE VENTRICULOGRAPHIC INDICES

<table>
<thead>
<tr>
<th></th>
<th>EF (%)</th>
<th></th>
<th>TES (msec)</th>
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<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>p value</td>
<td>Group 1</td>
</tr>
<tr>
<td>Global</td>
<td>59 ± 6</td>
<td>58 ± 5</td>
<td>NS</td>
<td>347 ± 23</td>
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<tr>
<td>Septal</td>
<td>74 ± 6</td>
<td>72 ± 11</td>
<td>NS</td>
<td>344 ± 30</td>
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<td>Apical</td>
<td>80 ± 7</td>
<td>77 ± 7</td>
<td>NS</td>
<td>349 ± 29</td>
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<tr>
<td>Lateral</td>
<td>75 ± 9</td>
<td>77 ± 7</td>
<td>NS</td>
<td>350 ± 27</td>
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<table>
<thead>
<tr>
<th></th>
<th>RFP/DT</th>
<th></th>
<th>%LDF (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>p value</td>
<td>Group 1</td>
</tr>
<tr>
<td>Global</td>
<td>0.49 ± 0.07</td>
<td>0.49 ± 0.06</td>
<td>NS</td>
<td>20 ± 5</td>
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<tr>
<td>Septal</td>
<td>0.50 ± 0.07</td>
<td>0.50 ± 0.05</td>
<td>NS</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Apical</td>
<td>0.46 ± 0.06</td>
<td>0.48 ± 0.05</td>
<td>NS</td>
<td>21 ± 4</td>
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<tr>
<td>Lateral</td>
<td>0.46 ± 0.07</td>
<td>0.43 ± 0.06</td>
<td>NS</td>
<td>22 ± 6</td>
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</table>

Values are mean ± SD. Group 1 = control subjects; Group 2 = patients with single-vessel disease. Abbreviations: EF = ejection fraction; TES = time to end-systole; RFP = rapid filling phase; DT = diastolic time; %LDF = percent contribution of late diastolic filling to total filling volume.
Reproducibility of Radionuclide Technique

The reproducibility of radionuclide ventriculographic variables obtained in this study was determined in 12 patients with various heart diseases (previous myocardial infarction (n = 3), angina pectoris (n = 3), hypertensive heart disease (n = 3), valvular heart disease (n = 2), and hypertrophic cardiomyopathy (n = 1)). Two separate radionuclide studies were performed 20 to 30 min apart on patients at rest after a single injection of technetium-99m. In the interval between the two studies the patients rested in the supine position. All the studies were performed at least 72 hours after all treatment had been stopped.

Angiographic Study

Hemodynamic data were obtained during cardiac catheterization, as previously described. Coronary angiographic examinations were performed by the Sones method.

Statistical Analysis

The data are presented as mean ± SD. The lower and upper limits of the normal values were defined as the mean ± 2SDs. Statistical analysis was performed with the t test for unpaired data. The level of statistical significance was p < 0.05.

RESULTS

Clinical and hemodynamic parameters are listed in Table I and radionuclide parameters in Table II. There were no significant differences between group 1 and group 2 in mean resting heart rate, mean diastolic time, or values for hemodynamic variables obtained during cardiac catheterization (Table I). There were also no significant differences in ejection fraction or time to end-systole in the global left ventricle or in any of the three regions (septal, apical, and lateral) between the two groups (Table II). To allow comparison of the time interval between global and regional rapid filling phase, the absolute value of the time interval was normalized by the global diastolic time, and the value obtained was expressed as a percentage. There were no significant differences in this value between the two groups in the septal (group 1, 3 ± 2%; group 2, 3 ± 2%; NS), apical (3 ± 2%, 2 ± 1%; NS), or lateral (4 ± 2%, 6 ± 4%; NS) regions. This also indicates that the time interval between global and regional rapid filling phase was short relative to the global diastolic time in both groups, and that each region terminated rapid filling phase and started late diastolic filling phase at nearly the same time as the global left ventricle in both groups. The percent contributions of late diastolic filling to total filling volume were significantly greater in group 2 than in group 1 in the global left ventricle, septal and apical regions, while there was no significant difference between the two groups in the lateral region (Fig. 2). However, there was a significant overlap in this value between the two groups. When an abnormal value was defined as one greater than 2SDs from the mean derived from 14 control subjects, of the 21 patients in
Fig. 3. Percent contribution of late diastolic filling to total filling volume. G2B = patients with a greater value (> 2SDs: 30% upper limit of the normal value in the global left ventricle) of the percent contribution in the global left ventricle in group 2. G2A = patients without this abnormal value in group 2. Abbreviations are the same as Fig. 2. Bars represent mean ± SD.

DISCUSSION

The values obtained for diastolic parameters should be interpreted with caution since addition of different cycle lengths affects the entire composite time-activity curve with the effect becoming greater toward the end of the curve. There are potential sources of error in our method stemming from the counts correction for undersampling at the terminal portion of the cardiac cycle.

Thus, the late diastolic phase of time-activity curves constructed with forward-gating radionuclide ventriculography was distorted and unreliable whenever a minimal variation of R-R interval was present. However, these sources of error probably did not affect our measurements of late diastolic variables since global and regional rapid filling phases terminated in the frames before the terminal 30% portion of the time-activity curves in all patients studied and values for global and regional late filling phases were obtained by subtracting values for rapid filling phases from total filling volume.

It has been suggested that left ventricular relaxation and compliance may be the major determinants of the left ventricular filling. Myocardial fibrosis or ischemia slows ventricular relaxation phase and may decrease ventricular compliance. Our patients studied had no previous myocardial infarction and resting myocardial scintigraphy with thallium-201 showed no uptake defects in any patients. However, in patients in group 2, small foci of myocardial necrosis produced by repeated anginal episodes, too small to be detected by resting myocardial scintigraphy, might have caused impairment of relaxation or compliance in the regions perfused by stenosed vessel. Thus, in the presence of regional ischemia or fibrosis, even though too small to be detected, it is possible that regional ventricular filling is impaired in regions perfused by stenosed vessel. In the present study, as expected in patients with single-vessel disease, the percent contributions of late diastolic filling to total filling volume were increased in regions perfused by stenosed vessel and the dependence on atrial systole for the left ventricular filling was supposed to increase in order to compensate the decreased early filling volume in these involved regions since a little

*Reproducibility of Radionuclide Measurements*

The reproducibility of global or regional left ventricular ejection fractions, times to end-systole has been reported previously. The reproducibility of the other radionuclide parameters obtained in this study was also excellent. The correlation between the first and second study was $r \geq 0.90$ for rapid filling phase/diastolic time, and was $r \geq 0.90$ for percent contribution of late diastolic filling to total filling volume.
Inhomogeneous Contribution of Late Diastolic Filling

Fig. 4. Typical global and regional time-activity curves obtained in a control subject (G 1) and a patient with single-vessel disease of the left anterior descending coronary artery (G 2), in which end-diastolic counts were expressed as 100% and minimum counts as 0% during a cardiac cycle. As shown by the arrow, the increased contributions of the late diastolic filling to the total filling volume were observed in the affected septal and apical regions and in the global left ventricle in a patient with single-vessel disease. Furthermore, the increased late diastolic filling in the global left ventricle may attribute to the increased late diastolic filling in the affected regions in patients with single-vessel disease (Fig. 3). Thus, the present results suggest that the late diastolic filling makes a larger contribution to the left ventricular filling volume in the affected regions than in the normally perfused regions and that the increased regional late diastolic filling in the affected regions results in the increased late diastolic filling in the global left ventricle in patients with single-vessel disease (Fig. 2, 3).

Although much more evidence should be necessary for understanding the mechanism of the increased contributions of the late diastolic filling to the total filling volume in the affected regions, the present results emphasize the clinical importance that impairment of the regional filling could occur in some patients with angina pectoris without myocardial infarction and that anginal episodes itself may alarm the initiation of the disturbance of the regional late diastolic performance.

Acknowledgement

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REFERENCES

5. YAMAGISHI T, OZAKI M, KUMADA T, IKEYOZNO T, SHIMIZU T, FURUTANI Y, YAMAOKA H, OGAWA H, MATSUZAKI M, MATSUDA Y, ARIMA A, KUSUKAWA R: Asynchronous left ventricular diastolic filling in...


16. GEFT IL, FISHEIN MC, NINOMIA K, HASHIDA J, Y-RIT ECJYJ, SHELL TGW, GANZ W: Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis. *Circulation* **66**: 1150, 1982