QUANTITATIVE ANALYSIS OF GLOBAL AND REGIONAL CARDIAC PERFORMANCE IN NORMAL SUBJECTS AND PATIENTS WITH CORONARY ARTERY DISEASE BY REST/EXERCISE RADIONUCLIDE BLOOD-POOL STUDY

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This study was undertaken to assess regional and diastolic left ventricular (LV) function in relation to LV asynchronous contraction during exercise (Ex).

Rest and serial Ex (25w-75w) gated blood-pool study (Tc-99m-RBC) of 6 normal subjects (N), 12 patients with stable angina pectoris (AP) and 8 with LV aneurysm (LVAn) were evaluated in regional LV ejection fraction (EF) and Fourier analysis using higher-order harmonics.

In the patients with Ex and regional EF showed various responses to Ex. Global LVEF in the patients with AP indicated almost no change during Ex and regional EF declined apparently in anteroseptal segment, corresponding to stenotic left anterior descending artery.

Diastolic indices of regional and global cardiac performance, PFR (peak filling rate), TPF (time to PFR) and standard deviation (SD) of TPF histogram, were obtained by Fourier analysis using two-order harmonics.

Patients with coronary artery disease (CAD) showed significantly lower PFR, longer TPF and higher SD of TPF than normal group, suggesting asynchronous relaxation.

We conclude that regional EF response and diastolic indices of cardiac performance to exercise provide useful and sensitive information detecting the severity of CAD.

THE assessment of regional left ventricular performance and wall motion is of particular interest in patients with coronary artery disease (CAD) and in some of these patients regional abnormalities may be detected only during exercise. Abnormal diastolic performance in patients with CAD has not always been associated with impaired systolic performance; it has occurred at rest even when acute ischemia or previous myocardial infarction was not found.1-3

The purpose of this study is to examine variables of changes in the left ventricular regional ejection fraction and diastolic left ventricular function at rest and during exercise in patients with CAD, using noninvasive methods are reliable and subtle markers of cardiac dysfunction.

Using a gated equilibrium radionuclide blood-
pool study, at rest and with symptom-limited supine bicycle exercise in normal subjects and patients with CAD, we:

(1) defined normal values of regional ejection fraction (EF) at rest and during exercise.

(2) described changes in regional EF at rest and during exercise in patients with stable angina pectoris and myocardial infarction with left ventricular (LV) aneurysm.

(3) investigated the peak left ventricular filling rate (PRF) and the timing at rest and peak exercise in these subjects.

**MATERIAL AND METHODS**

**Patients population**

Group 1 consisted of 6 normal control volunteers (aged 27 ± 3 years), all male, without symptoms or signs of systemic disease. No subjects were taking medications and each had a normal resting radionuclide (RI) left ventricular ejection fraction (LVEF), electrocardiograms, and physical examination.

Group 2 consisted of 12 patients with stable angina pectoris (aged 50 ± 11 years), angiographically documented proximal stenosis (> 75 %) of the left anterior descending (LAD), or the left circumflex (LCX) coronary artery (single vessel disease) and both coronary arteries (double vessels disease). Four of these had previous antero septal myocardial infarction with a history of chest pain, an elevated serum creatinine kinase level, and characteristic electrocardiographic changes at least 6 months previously. None of the patients had evidence of valvular heart disease.

Group 3 consisted of 8 patients with myocardial infarction (aged 50 ± 8 years), most of whom had subtotal or total LAD occlusion with a broad left ventricular aneurysm with paradoxical wall-motion by RI-phase image at least 2 months previously and a depressed RI LVEF at rest (<40%).

**Equilibrium radionuclide blood-pool study**

All studies were performed with a scintillation camera (HITACHI Gamma-VIEW-H), with the gamma-detector placed at the 45° left anterior oblique position. A general-purpose collimator was used in all studies, and the photoprobe of the camera was set at 140 KeV with a 20% window.

Multiple gated equilibrium radionuclide blood-pool studies were performed by in vivo labeling of red blood cells with 20 mCi Tc-99m.

Radionuclide data were accumulated at rest and continuously during exercise for LVEF, and quantitation of regional and global left ventricular performance by phase analysis using higher-order harmonics, with a commercially available nuclear medicine computer system (Sopha Informatek Simis III). The cardiac cycles of a 2 min. acquisition period at rest or during exercise were assembled at corresponding times to generated composite images throughout the heart cycle.

EF was calculated from the time-activity curve according to the formula: EF(%) = [(CVD−CES)/CED] × 100 where CED = left ventricular counts at end-diastole and CES = left ventricular counts at end-systole, each corrected for background.

For regional EF, the computer determined a center of gravity of the left ventricular activity at end-diastole. From this center, eight radial sectors of 45° were defined. Because of overlap with the aorta and/or left atrium, three of these eight sectors were excluded from further analysis.

The remaining five sectors were assigned to the three main coronary arteries: Two anteroseptal sectors to the left anterior descending coronary artery (LAD) and two posterolateral sectors to the left circumflex coronary artery (LCX). There was only one inferoapical sector in the LAD view which is normally perfused by the right coronary artery (RCA). The change in counts from end-diastole to end-systole in each sector was used to calculate regional EF similar to the calculation of global LVEF.

Separation of systolic and diastolic parameters in gated radionuclide blood-pool study was achieved with retention of two-order harmonics in the Fourier-series representation of the time-activity curve (TAC).

\[ TAC(t) = a_0 + a_1 \cos(\omega t - \phi_1) + a_2 \cos(\omega t - \phi_2) \]  \hspace{1cm} (1)

The first derivative of each single-pixel time-activity curve was determined by analytically differentiating Eq (1).

\[ \frac{d}{dt} [TAC(t)] = -a_1 \omega \sin(\omega t - \phi_1) - 2 \]  \hspace{1cm} (2)

Then the peak ejection rate (PER), time to peak ejection rate (TPE), the peak filling rate (PFR) and time to peak filling rate (TPF) were determined for each pixel from the time-activity curve and first-derivative curve. Rates were expressed in units of end-diastolic-volumes/sec (EDV/sec) and time intervals in msec.

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were generated to facilitate interpretation of the regional variations in time and rate parameters within the left ventricle. The spread of each of these factors was measured by the standard deviation of the histogram (for example: SD of PFR histogram, SD of TPF histogram).

The rate and time parameters were computed for the left ventricular taken as a whole as well as regionally. The global left ventricular time-activity curve was obtained with an ejection fraction program. The preceding measurements (PER, TPE, PFR, TPF) were retained in the Fourier-series of analysis of the global data.

Exercise studies

Normal subjects and all patients underwent supine bicycle exercise on an ergometer up to serial level from 25w to 75w or a level to produce exercise limiting symptoms.

The position of the scintillation camera was not changed between rest and exercise studies. ECG and blood pressure were monitored during the exercise test. Data from the last 2 minutes of exercise were used to calculate global and regional EF and diastolic left ventricular function.

RESULTS

Response of global EF and regional EF to exercise

Global EF of all Group I subjects increased during exercise from 60.3 ± 4.1 to 65.5 ± 2.9 (N.S.). Normal values of regional EF at rest and peak exercise are shown in Fig. 1 and summarized in Table I. At rest, regional EF was significantly lower in the anteroseptal than in the other two areas (p < 0.01). During exercise, regional EF increased significantly in the anteroseptal and inferoapical areas (p < 0.05), but decreased in the posterolateral area in a few normal subjects.

On the other hand, patients in Group 2 had almost no change in global EF, in comparison with that of Group I subjects and normal regional EF at rest, but an apparent decrease of the anteroseptal regional EF, corresponding to stenotic LAD, during exercise.

In patients of Group 3, global EF was depressed at rest and increased slightly with exercise; also regional EF response to exercise indicated various patterns.

Diastolic filling indices at rest and during exercise (Table II)

The results of the global analysis of peak filling rate (PFR) at rest and peak exercise are shown in Fig. 2 for each subject in all groups. At rest, none of the normal subjects had PFR less than 1.5 EDV/sec, although 5/12 (41%) of the Group 2 patients, especially with myocardial infarction had filling rate below this level and 6/8 (75%) of Group 3 patients had subnormal PFR.

With exercise, all 3 groups showed significant increases in PFR but, once again, Group 3 patients tended to have lower values compared with the normal subjects.

Analysis of timing variables (Table II, Fig. 3)

The R-R interval was arranged in order of increasing distance in Groups 3, 1 and 2, at rest.
TABLE I  GLOBAL AND REGIONAL LVEF MEASUREMENTS AT REST AND PEAK EXERCISE OF TWO PATIENTS GROUPS IN COMPARISON WITH NORMAL VALUES

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Ex</th>
<th>Rest</th>
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<th>Rest</th>
<th>Ex</th>
<th>Rest</th>
<th>Ex</th>
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<tr>
<td>Global LVEF</td>
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<tr>
<td>Noramls. (n = 6)</td>
<td>60.3 ± 4.1</td>
<td>65.5 ± 2.9</td>
<td>61.9 ± 5.6</td>
<td>73.3 ± 3.7</td>
<td>80.0 ± 3.7</td>
<td>87.8 ± 4.5</td>
<td>86.1 ± 6.3</td>
<td>84.6 ± 6.5</td>
</tr>
<tr>
<td>Stable angina pectoris (n = 12)</td>
<td>55.9 ± 14.5</td>
<td>57.7 ± 14.5</td>
<td>60.9 ± 20.5</td>
<td>56.7 ± 20.7</td>
<td>72.5 ± 18.1</td>
<td>78.2 ± 19.4</td>
<td>81.5 ± 11.4</td>
<td>82.3 ± 14.0</td>
</tr>
<tr>
<td>Myocardial infarction with LV aneurysm (n = 8)</td>
<td>28.9 ± 12.1</td>
<td>32.1 ± 9.9</td>
<td>27.1 ± 7.2</td>
<td>30.7 ± 7.4</td>
<td>40.4 ± 15.6</td>
<td>40.3 ± 19.5</td>
<td>53.8 ± 17.3</td>
<td>59.1 ± 19.5</td>
</tr>
</tbody>
</table>

P values pertain to changes from rest to exercise.

TABLE II  VARIABLES DESCRIBING LEFT VENTRICULAR DIASTOLIC FUNCTION IN NORMAL SUBJECTS AND PATIENTS WITH CAD AT REST PEAK EXERCISE (EX)

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak Ex.</th>
<th>Rest</th>
<th>Peak Ex.</th>
<th>Rest</th>
<th>Peak Ex.</th>
<th>Rest</th>
<th>Peak Ex.</th>
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<tbody>
<tr>
<td>Normal (n = 6)</td>
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<tr>
<td>LV global PFR (EDV/sec)</td>
<td>1.96 ± 0.247°</td>
<td>3.77 ± 0.537*</td>
<td>1.76 ± 0.646</td>
<td>3.51 ± 0.996**</td>
<td>1.12 ± 0.470°</td>
<td>2.31 ± 0.523**</td>
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<tr>
<td>SD of PFR histogram (LV regional PFR)</td>
<td>1.33 ± 0.087</td>
<td>2.47 ± 0.437</td>
<td>1.26 ± 0.235</td>
<td>2.53 ± 0.806</td>
<td>1.56 ± 0.755</td>
<td>2.42 ± 0.421</td>
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<tr>
<td>LV global TPF (msec)</td>
<td>153.2 ± 13.1</td>
<td>144.4 ± 29.0</td>
<td>168.7 ± 23.4</td>
<td>139.4 ± 17.7</td>
<td>220.9 ± 89.4</td>
<td>134.8 ± 23.0</td>
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<tr>
<td>LV global TRF/R-R</td>
<td>17.2 ± 1.7</td>
<td>25.5 ± 4.6</td>
<td>17.2 ± 2.9</td>
<td>24.5 ± 1.7</td>
<td>27.7 ± 11.3</td>
<td>24.4 ± 4.9</td>
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</tr>
<tr>
<td>SD of TPF histogram (LV regional TPF)</td>
<td>78.3 ± 18.1</td>
<td>49.8 ± 11.7</td>
<td>114.2 ± 43.1</td>
<td>55.9 ± 12.6</td>
<td>153.0 ± 56.6</td>
<td>79.1 ± 34.1</td>
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</table>

Data are mean ± SD  p < 0.01 °, *, PER = peak filling rate TPF = time to peak filling.
During exercise the R-R intervals were shorter and not different among the groups.

Time to peak filling rate (TPF) at peak exercise was shorter than at rest in CAD patients (p < 0.01). But normalization by R-R interval reversed these relationships.

CAD (Group 2 and 3) patients showed a significantly larger standard deviation of the TPF histogram than Group 1 (p < 0.05), indicating regional nonhomogeneity of filling (asynchronous relaxation).

At peak exercise, the SD of these TPF histograms was smaller than at rest (p < 0.01~0.02), suggesting significant improvement in regional asynchrony.

Relation of filling rates to ejection fraction

The rest and exercise peak filling rates are shown as a function of the corresponding rest and exercise ejection fraction for all patients in Fig. 4. There was a significant correlation between these 2 variables both at rest (r = 0.71, p < 0.01) and at peak exercise (r = 0.83, p < 0.01).

DISCUSSION

In patients with CAD, quantitative assessment of regional changes in left ventricular contraction became very important in differentiating between normal and ischemic segments.

Area, chord and radial methods, which had been used for contrast ventriculography, were applied to radionuclide blood-pool study at rest. In the present study, we validated a radial method for the regional ejection fraction calculation from short acquisition of equilibrium radionuclide blood-pool study in normal subjects and patients with CAD.

The result of the regional ejection fraction at rest showed lower values for the anteroseptal region as compared with the other two. In previous radionuclide studies others have noted a similarly reduced motion of the septal wall or lower function in that region.

There may be a methodological explanation of the lower regional function in the anteroseptal area in our analysis: we used a center of...
Fig. 3. SD of TPF histogram (LV regional TPF) at rest and exercise in normal subjects and patients with CAD.

Exercise
\[ y = 0.0474x + 0.68 \]
\[ n = 26 \]
\[ (r = 0.826 \quad P < 0.01) \]

Rest
\[ y = 0.0245x + 0.46 \]
\[ n = 26 \]
\[ (r = 0.708 \quad P < 0.01) \]

Fig. 4. Correlation of ejection fraction and peak filling rate at rest and peak exercise for the entire study population.

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Also, we observed a significant correlation between LVEF and PFR in all normal subjects and patients at rest and peak exercise. A similar relationship had been described by others.\(^5,9\)

In the present study, emphasis was placed on analysis of regional as well as global left ventricular dysfunction. Manifestation of CAD in diastole was regional in character, just as the systolic manifestations were\(^12\) therefore, the earliest manifestation of abnormal diastolic performance might be regional. At rest, the stable angina and the LV aneurysm groups had significantly non-homogeneous regional diastolic filling times, as represented by high values in the standard deviation of TPF histogram, as seen in Table II and Fig. 3. Thus, regional analysis of the time to peak filling could detect coronary artery disease, manifested by left ventricular diastolic abnormalities. With exercise, those differences disappeared when the R-R interval was normalized.

In conclusion, the results reported here indicated that regional as well as global left ventricular diastolic behavior could be characterized quantitatively by noninvasive analysis of diastolic function, providing a sensitive and practical means for detection of CAD.

Acknowledgment

The investigations were supported by the Grant from Kekyo-Kai Research Foundation No.58-6.

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