RELATIONSHIP BETWEEN THE RELATIVE REGIONAL THALLIUM-201 UPTAKE AND THE REGIONAL SYSTOLIC OR DIASTOLIC FILLING FUNCTION

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Both the resting thallium-201 imaging and resting gated radionuclide ventriculography were conducted in the left anterior oblique view in 35 patients with isolated disease of the left anterior descending coronary artery (LAD), and the corresponding involved region was compared from two differing perspectives, one measuring regional ventricular function and the other regional myocardial perfusion. In the thallium-201 imaging, the thallium activity in the septal or apical region supplied by the LAD was calculated as an activity ratio between the mean value of the normally perfused lateral region and that of the septal or apical region, and was called relative thallium uptake (%Tl uptake). In the gated radionuclide ventriculographic study, a computer program subdivided the image of the left ventricle into 4 regions. The time-activity and first-derivative curves were computed in the septal and apical regions. Significant positive correlations were present between the %Tl uptake and the ejection fraction or peak ejection rate both in the septal and apical regions, indicating that the regional systolic function diminishes progressively as the perfusion abnormality increases. However, positive but poor and scattering correlations were found between the %Tl uptake and the peak filling rate, and there were no significant correlations between the %Tl uptake and the filling period in these affected regions.

Thus, we could suppose that the regional systolic function is closely related to the regional %Tl uptake which probably reflects the amount of the residual viable myocardium, but there is the possibility that the regional diastolic filling function may be not so much related to the amount of the viable myocardium as is systolic function or may be modulated by some factors other than the amount of the regional viable myocardium.

THE relationship between regional myocardial blood flow and regional systolic function has been extensively studied in experimental models and it has been observed that the regional

systolic dysfunction during acute transient ischemia is related to the reduction in myocardial blood flow both at the steady resting state¹⁻⁶ and during exercise-induced ischemia^{6,7}. It has also been observed that global left ventricular (LV) systolic function deteriorates in proportion to the increase in the size of the infarct.⁸⁻¹⁴ However, there are few data comparing the ex-

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Fig.1. Left: The resting myocardial image was divided into 36 sections, each separated by 10° , with 36 radii extending from the centroid of this image. We arbitrarily defined the segment between 140° and 220° (No. 14 to 22 on the inner numbers) along the outer border of the myocardial image as the septum, the segment between 230° and 310° (No. 23 to 31) as the apical wall, and the segments between 0° and 40° (No. 0 to 4) and between 320° and 350° (No. 32 to 35) as the lateral wall. The mean values for the percent normalized thallium activity (outer numbers) were calculated for the 3 segments.

Right: The left ventricular region of interest at end-diastole was separated into 4 regions at the geometric center of the area. The background correction was estimated in each of the septal, apical, and lateral regions of interest obtained at end-systole, as shown in this figure.

tent of the regional perfusion abnormality and the severity of the regional diastolic filling dysfunction. The specific question is whether the extent of the regional perfusion abnormality relates to the regional diastolic filling dysfunction in the same manner that the severity of the regional perfusion abnormality relates to the regional systolic dysfunction. Resting thallium-201 myocardial imaging provides information about regional myocardial perfusion¹⁵⁻¹⁷ and myocardial scar,^{13,18,19} since myocardial thallium-201 uptake is generally considered to be in proportion to the regional viable myocardium.^{18,19}

The aim of the present study is to clarify the relationship between the magnitude of the perfusion abnormality at the steady resting state and the degree of LV regional systolic function or diastolic filling function using resting thallium-201 scintigraphy and resting gated radionuclide ventriculography in 35 patients with angiographically-proven isolated disease of the left anterior descending coronary artery. In the present study, emphasis is placed on analysis of the relationship between the magnitude of the regional perfusion abnormality and the extent of the regional diastolic filling dysfunction.

Patient selection

The study group consisted of 35 patients with significant isolated disease of the left anterior descending coronary artery (30 men and 5 women, age range 35 to 71 years, mean age 55 ± 8 years). They underwent resting radionuclide ventriculography after the end of resting thallium-201 myocardial scintigraphy on the same day as part of their clinical evaluation of coronary artery disease. On coronary arteriography, all of the patients had organic coronary artery stenosis ($\geq 75\%$ luminal diameter) of only the proximal or mid portion of the left anterior descending branch. Seventeen patients had evidence of previous myocardial infarction diagnosed by typical chest pain, typical rise and fall of the serum creatine kinase level, serial electrocardiographic changes and resting images of thallium-201 myocardial scintigraphy. The other 18 patients had frequent anginal episodes but no evidence of previous myocardial infarction. All patients underwent the radionuclide studies and the cardiac catheterization within one month of each other and the patients with previous myocardial infarction underwent these tests at least one month after the onset of typical chest pain, so that the increase in sympathetic activity associated with acute myocardial infarction would have normalized by this time. Patients with

Fig.2. Regional relative thallium uptake versus regional ejection fraction at the resting state. Bars represent mean $\pm$ 2SDs derived from normal subjects.

other associated cardiac abnormality, hypertensive heart disease or additional coronary lesions were excluded from the study. Radionuclide studies were performed at least 72 hours after treatment with calcium antagonists or beta-blockers had been stopped and at least 12 hours after treatment with nitrates was stopped. At the time of radionuclide studies, no patients had angina for at least 6 hours. All patients fasted for approximately 6 hours prior to the radionuclide studies.

The reason why we selected patients with a single vessel disease is that the regional myocardial perfusion and the regional ventricular function are more easily interpreted in a single vessel disease than in a multiple vessel disease and this myocardial perfusion and ventricular function in the affected regions is easily compared with that in the normally perfused regions.

Resting thallium-201 scintigraphy

Each patient received a dose of 3–4 mCi of thallium-201 as a bolus into the brachial vein at rest. Myocardial imaging was started in the resting state 10 min after the injection of thallium-201 using standard technique. A conventional gamma camera (PHO/GAMMA LFOV, Searle Inc., Des Plaines, IL) equipped with a high-resolution all-purpose parallel-hole collimator was used to acquire the images in a “best septal” 40° to 60° left anterior oblique view, selected so that the septum and lateral walls were vertically oriented. A 25% energy window centered on the 80 KeV X-ray photopeak was used for data recording. Acquisition was continued for a total of 600,000 counts in the full field of the gamma camera, and images were stored on a magnetic disk in a 64 $\times$ 64 matrix for subsequent analysis by a minicomputer (SCINTIPAC-

1200, Shimadzu Seisakusho, Kyoto, Japan).

Each image was smoothed using a nine-point averaging algorithm and was then corrected by means of Goris’ background subtraction technique²⁰. Then, a region-of-interest (ROI) was traced manually with an electronic cursor along the outer border of the processed myocardial contour (Fig. 1). After the centroid of this ROI was located manually, the ROI was divided into 36 sections, each separated by 10°, with 36 radii extending from the centroid of this ROI to the outer edge of this ROI.

The division was started from the lateral segment of this ROI with the radius extending parallel to the x coordinate of the digital matrix and proceeded counter-clockwise around the circumference. Then, the distribution of the thallium-201 activity within the ROI was determined by calculating the maximum activity per pixel along each radius, and by normalizing the data to the radius with the maximum activity among the 36 radii, and was expressed as a percent of the greatest pixel activity among the 36 radii. The 40° to 60° left anterior oblique view most clearly separates the three major coronary arterial perfusion beds. Coronary territories in myocardial segments were assigned in the following manner: the left anterior descending coronary artery supplies septal and apical segments, left circumflex coronary artery a lateral segment, and the right coronary artery an apical segment. As shown in Fig. 1, we arbitrarily defined the segment between 140° and 220° along the outer border of the myocardial image as the scintigraphic septum, the segment between 230° and 310° as the apical wall, and the segments between 0° and 40° and between 320° and 350° as the lateral wall, and the mean values for the percent normalized thallium activity were

Fig.3. Regional relative thallium uptake versus regional peak ejection rate. Bars represent mean $\pm$ 2SDs derived from normal subjects.

calculated for the 3 segments corresponding to the scintigraphic septum, lateral wall, and apical wall, and were called relative thallium uptake. These 3 left anterior oblique thallium segments were matched to the corresponding same degree left anterior oblique radionuclide ventriculographic segments to compare the regional thallium perfusion with the regional systolic function or the regional diastolic filling function.

Resting gated radionuclide ventriculography

Multigated equilibrium blood pool imaging was performed with the same conventional gamma camera and the collimator used in the resting thallium imaging. The technique used in this study was reported previously.^{21,22} Briefly, all patients were studied while quietly lying supine, and were given 15–20 mCi of technetium-99m-labelled human serum albumin. After the radionuclide had equilibrated with the intravascular space (about 10 min), the position of the camera was adjusted in the modified 40° to 60° left anterior oblique projection (15° caudal tilt). Images were obtained in a multiple-gated mode on a magnetic disc with the same computer system used in the resting thallium imaging. Counts were acquired during 600 beats. Those photoevents falling within a 20% window centered on the photopeak of technetium-99m were recorded. A computer-based procedure gated to the electrocardiogram was used to collect and organize data into a series of images or frames (framing rate up to 31 frames/cardiac cycle) spanning the average cardiac cycle.

The original multiple-gated mode data were

collected on a magnetic disc with a 64 × 64 matrix. Each 30 to 40 msec frame contained more than 30,000 counts within the left ventricle in the end-diastolic frame in all patients studied. 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.

A computer program determined a geometric center of the area of the end-diastolic perimeter of the left ventricle, and subdivided it into 4 regions (basal, septal, apical, and lateral), with 2 intersecting lines at an angle of 45° to the longitudinal axis of the left ventricle at the geometric center of the area (Fig. 1). Crescent-shaped regional background regions of interest were traced manually with an electronic cursor along the lateral, apical and septal portions applied to the end-systolic frame, specifically avoiding regions of high-count activity according to the method described previously (Fig. 1).^{21,22} Background correction for the 3 regions (septal, apical, and lateral regions) was estimated with an average count per pixel in each of the 3 background regions of interest. Background-corrected regional time-activity curves were generated after three-point temporal smoothing using a fixed region of interest method. First-derivative curves (dV/dt) of these time-activity curves were computed in the 3 regions.^{21,22} A maximal value of positive dV/dt during diastole was defined as the peak LV filling rate. End-systole was defined as the minimal volume at which the dV/dt value was

Fig.4. Regional relative thallium uptake versus regional peak filling rate. There were positive but poor and scattering correlations between these two variables. Bars represent mean $\pm$ 2SDs derived from normal subjects.

0. A minimal value of negative dV/dt during systole was defined as the peak LV ejection rate. Since the basal region of the left ventricle tended to overlie the regions of mitral and aortic valves, aorta, left atrium, and great vessels, this region was excluded from study.

The following indexes were obtained regionally.

Systolic phase indexes

(1) Ejection fraction(%) = $100 \times (\text{end-diastolic counts} - \text{end-systolic counts}) / (\text{end-diastolic counts} - \text{background counts})$.

(2) Peak ejection rate (end-diastolic counts/sec, EDV/sec) = peak ejection rate normalized to end-diastolic counts.

Diastolic phase indexes

(1) Peak filling rate (end-diastolic counts/sec, EDV/sec) = peak filling rate normalized to end-diastolic counts.

(2) Time to peak filling rate/diastolic time = interval between the global end-systole and the peak positive dV/dt was normalized to diastolic time (RR interval - time interval between the R wave and the global end-systole (systolic time)), since heart rate or diastolic time affects measurement of diastolic variables.²¹⁻²³

Reproducibility of variables measured in this radionuclide ventriculographic study was reported and validated in patients with and without regional LV wall motion abnormalities.^{21,22}

Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD). The lower and upper limits of the

normal values were defined as the mean $\pm$ 2SDs determined in 15 normal subjects in our previous study.²¹ Statistical analysis was performed with the t-test for unpaired data. The level of statistical significance was $p < 0.05$. Relations between resting relative thallium uptake and radionuclide ventriculographic indexes of systolic function or diastolic filling function were expressed in terms of linear regression correlation coefficient.

RESULTS

Normal data

Ejection fractions in 15 normal subjects studied previously in our laboratory were $72 \pm 9\%$, $81 \pm 8\%$ and $74 \pm 9\%$ in the septal region, apical region and lateral region, respectively.²¹ Peak ejection rates in each of the aforementioned 3 regions were 3.76 ± 0.77 , 4.62 ± 0.96 and 4.43 ± 0.88 EDV/sec, respectively. Peak filling rates were 3.64 ± 0.72 , 4.42 ± 1.03 and 4.24 ± 0.74 EDV/sec, respectively.²¹ Times to peak filling rate/diastolic time were 0.35 ± 0.05 , 0.33 ± 0.05 and 0.28 ± 0.05 , respectively. The mean relative thallium uptakes in 10 normal subjects in our laboratory were $96 \pm 13\%$ in the septal region and $97 \pm 10\%$ in the apical region.

Patient data

Relative thallium uptake ranged from 8 to 115% in the septal region (mean $71 \pm 26\%$) and from 20 to 125% in the apical region (mean $79 \pm 26\%$). Ejection fraction ranged from 27 to 93%, from 33 to 87%, and from 49 to 85% in the septal, apical, and lateral region, respectively. Significant positive correlations were found be-

Fig. 5. Regional relative thallium uptake versus regional time to peak filling rate/diastolic time. There were no significant correlations between these two variables. Bars represent mean $\pm$ 2SDs derived from normal subjects.

tween the relative thallium uptake and the ejection fraction in the septal region ($r = 0.66$, $p < 0.001$) and in the apical region ($r = 0.81$, $p < 0.001$) (Fig. 2), with a greater reduction in the relative thallium uptake with more reduced ejection fraction. Peak ejection rate ranged from 1.48 to 5.92, from 1.44 to 5.15, and from 2.32 to 4.81 EDV/sec in the septal, apical and lateral region, respectively. There were also significant positive correlations between the relative thallium uptake and the peak ejection rate in the septal region ($r = 0.52$, $p < 0.01$) and in the apical region ($r = 0.74$, $p < 0.001$) (Fig. 3). These results indicate that the regional systolic function diminishes progressively as the extent of the perfusion abnormality increases.

Peak filling rate ranged from 1.36 to 4.71, from 0.85 to 4.87, and from 1.94 to 5.02 EDV/sec in the septal, apical and lateral region, respectively. Significant but poor and scattering positive correlations were found between the relative thallium uptake and the peak filling rate in the septal region ($r = 0.42$, $p < 0.05$) and in the apical region ($r = 0.53$, $p < 0.01$) (Fig. 4). Time to peak filling rate/diastolic time ranged from 0.26 to 0.56, from 0.26 to 0.58, and from 0.19 to 0.43 in the septal, apical and lateral region, respectively. No significant correlations were observed between this filling period and the relative thallium uptake both in the septal region ($r = 0.20$) and in the apical region ($r = 0.21$) (Fig. 5).

DISCUSSION

In this study, both the resting thallium imaging

and the resting radionuclide ventriculography were performed two-dimensionally in the same left anterior oblique view with the standard planner approach, and the corresponding involved region was compared from two differing perspectives, one measuring regional ventricular function and the other regional relative thallium uptake.

Regional systolic function versus relative thallium uptake

Significant positive correlations were present between the relative thallium uptake and the LV systolic function at the steady resting state in the involved septal and apical regions, indicating that the regional systolic function diminishes progressively as the extent of the perfusion abnormality increases (Figs. 2 and 3). The present regional systolic function data confirm previous correlations of the regional systolic function and the regional perfusion abnormality.¹⁻¹⁴ The initial thallium uptake at rest has been reported to be related to tissue viability,^{18,19} to regional myocardial blood flow,¹⁵⁻¹⁷ and to histopathological and histochemical assessment of myocardial necrosis,¹⁸ and the magnitude of thallium perfusion abnormalities has been reported to correlate semiquantitatively with the extent of LV systolic function in man.¹³ Thus, it is reasonable to conclude from our study that the systolic function in the involved regions correlates positively with the amount of the residual viable myocardium, since the relative regional thallium uptake obtained in this study probably reflects the amount of the residual viable myocardium.^{18,19}

Regional diastolic filling rate versus relative thallium uptake

The major new finding of the present study was that the positive but poor and scattering correlations were present between the relative thallium uptake and the peak filling rate in the regions supplied by the left anterior descending coronary artery (Fig. 4). This result suggests that there may be the possibility that the regional diastolic filling rate is not so much related to the relative regional thallium uptake as is systolic function. This may be, in part, well understood in the light of the fact that the regional diastolic filling rate is already impaired even in the regions where the regional systolic function and regional myocardial blood flow are normally preserved.²¹

The mechanisms or factors responsible for the poor correlation between the relative regional thallium uptake and the regional peak filling rate are not clear. Relaxation of cardiac muscle is an energy-dependent process,²⁴ and it has been reported that the impairment of the rate of LV relaxation correlates positively with the severity of the systolic impairment.²⁵⁻²⁷ This suggests that the rate of LV relaxation is impaired progressively as the amount of the residual viable myocardium is decreased. On the other hand, relaxation of cardiac muscle has been reported to be one of the most important determinants of the early diastolic filling and several investigators have noted that the rate of LV relaxation is found to be correlated with the diastolic peak filling rate.²⁹⁻³¹ Combined with these findings, one could suppose that the diastolic peak filling rate is correlated with the amount of the viable myocardium.

Bashore et al²⁸ have shown that a positive correlation exists between the peak filling rate and the ATP content from simultaneously obtained LV biopsy specimens, which also suggests the possibility of the positive correlation between the amount of the viable myocardium and the peak filling rate. In agreement with these previous observations, in the present study, positive but poor and scattering correlations were found between the relative thallium uptake and the peak filling rate in the affected regions. These poor and scattering correlations may suggest that the peak filling rate may be poorly affected by the amount of the viable myocardium or may be modulated by some additional factors other than the amount of the viable myocardium, since, unlike the LV relaxation, the peak filling rate occurs after the opening of the mitral valve, so

that there is the possibility that some factors other than the LV relaxation may act in the diastolic filling process. Thus, we could suppose that the diastolic filling rate may be poorly affected by the amount of the viable myocardium or may be modulated by some factors other than the amount of the residual viable myocardium.

Regional diastolic filling period versus relative thallium uptake

There are few reports comparing the magnitude of the myocardial perfusion and the diastolic filling period. In this study, no significant correlations were found between the relative thallium uptake and the time to peak filling rate/diastolic time in the regions supplied by the left anterior descending coronary artery (Fig. 5), which suggests that the filling period may not be affected by the amount of the viable myocardium or may be modulated by some factors other than the amount of the residual viable myocardium.

It is well known that in patients with coronary artery disease the regional time to peak filling rates in the affected regions occur later than those in the normally perfused regions even when the regional systolic function is normally preserved.^{21,22} When the regional time to peak filling rates/diastolic time in the regions with depressed regional ejection fraction (group 1) (< 2 SDs from the normal mean; $< 54\%$ for the septal region, $< 65\%$ for the apical region) were compared with those in the regions with the normally preserved regional ejection fraction (group 2), there were no significant differences in this value between the 2 groups in the septal region (group 1, $n = 13$; 0.40 ± 0.05 , group 2, $n = 22$; 0.41 ± 0.08) and in the apical region (group 1, $n = 11$; 0.37 ± 0.06 , group 2, $n = 24$; 0.38 ± 0.08). This suggests that the delay to peak LV filling in the affected regions occurs in the early stage of the development of coronary artery disease even when the regional systolic function is normally preserved, and that the occurrence of the regional peak LV filling is no more delayed when the regional systolic function is severely depressed in association with the myocardial infarction.^{21,22} This may, in part, account for no correlations between the relative thallium uptake and the filling period in the affected regions.

Potential limitations of this study

Although many methods have been proposed to quantitate the myocardial thallium uptake,

no technique definitely assesses the absolute myocardial thallium uptake, and we have no established methods to quantitate the absolute amount of viable myocardium in the clinical studies.

In this study, the activity in each segment was calculated as an activity ratio between the mean value of the lateral region and that of the involved septal or apical region. The lateral segment was used as a normally perfused region according to the coronary artery finding, against which the involved septal and apical segments were compared, so that the relative thallium uptakes in the involved but not underperfused septal or apical region showed more than 100% in some regions.

The subdivision of the left ventricle into 4 smaller regions was performed automatically by a computer program. This clearly did not take into consideration individual differences in LV anatomy, rotation, or magnitude of infarcted myocardium among patients. In some patients, there may be considerable overlap of the previously infarcted myocardium into the lateral region. This would reduce actual thallium uptake counts or LV systolic and diastolic functions in the normally perfused lateral region. Furthermore, there may be some overlap of the LV basal region into the septal or lateral region. The basal thallium activity is normally reduced because of the presence of the aortic or mitral valves. This would also reduce actual thallium uptake counts in the septal or lateral region.

Errors may also occur with the inability of the thallium image to detect scars of small size. Small sized infarction or nontransmural infarction might not have been represented as clear-cut thallium defects and might have failed to demonstrate defects in thallium uptake, since image resolution is limited in this study. Quantitative infarct imaging with single photon emission computed tomography has been shown to be a more sensitive detector of prior myocardial infarction than traditional planar imaging.³² By this technique, we may be able to measure subtle abnormalities of perfusion defect.

Although defects in the resting thallium images generally represent prior myocardial infarction, whether the segments which show thallium defects represent scar tissue or ischemia but viable myocardium is still a controversial issue.^{33,34} This may also result in one of the causes of the poor or no correlation between the relative thallium uptake and the diastolic filling

function, since there is the possibility that a discrepancy may exist between the thallium uptake and the ventricular function in these affected regions.

Finally, the peak filling rates and filling periods are only two factors in the diastolic filling process, and do not necessarily predict the entire properties of the diastolic filling function, so that further studies are needed to clarify the relation between the viable myocardium and the filling function.

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