《原　著》

Quantitative Assessment of Myocardial Perfusion Imaging with Thallium-201

——Basic Study and Its Clinical Applications——

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ABSTRACT To make a quantitative evaluation of myocardial perfusion images using thallium-201 we developed myocardial Tl uptake index. The Tl uptake index is defined as a ratio of Tl activity measured at the various parts of the background-subtracted myocardial images to the total injected Tl activity. Animal experiments (coronary artery ligated dogs) indicated that the Tl uptake index reflects myocardial Tl concentration as well as myocardial perfusion.

In 35 patients with angiographically demonstrated coronary artery disease, studies of myocardial perfusion with Tl, under exercise, have shown that the application of the Tl uptake index improves diagnostic sensitivity of coronary artery disease from 66% to 74%. In ten patients with coronary artery disease, myocardial Tl imaging and RI-angiocardiography with Tc-99m were obtained before and after the administration of nitroglycerin. And the study suggests, in some patients with coronary artery disease, enhancement of regional myocardial perfusion occurs following administration of the drug.

Clinical applications of the Tl uptake index are effective to evaluate the changes of myocardial perfusion under various investigations.

In recent years, myocardial perfusion imaging with thallium-201 (Tl) has been used for the evaluation of the regional myocardial perfusion and perfusion reserve in patients with coronary artery disease[1,2].

Animal experiments revealed that myocardial Tl concentration reflected myocardial blood flow under normal and ischemic conditions[3-5]. However it is not clear whether the regional myocardial tracer concentration obtained by imaging reflects the regional myocardial perfusion quantitatively, because myocardial images are expressed as net Tl concentration of myocardial and background activity.

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Besides, it is often difficult to evaluate small changes in the regional myocardial tracer concentration by visual inspection, especially when images are obtained at control and at stress. Therefore, we developed the myocardial Tl uptake index to quantitate the regional myocardial Tl concentration. And we studied whether the Tl uptake index reflected the regional myocardial perfusion by coronary artery ligated dogs.

Furthermore, we evaluated the validity of the Tl uptake index in myocardial imaging under exercise stress and myocardial imaging following nitroglycerin administration.

Materials and Methods

A Pho/Gamma HP scintillation camera equipped with 15000 parallel hole, high resolution, low energy collimator was used, and it was interfaced to a minicomputer (Scintipac 230). The camer

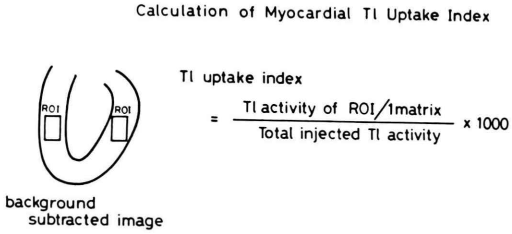

Fig. 1 Method of calculation of myocardial Tl uptake index. Tl uptake index was computed as ratio of Tl activity at various parts of background-subtracted myocardial image to total injected Tl activity.

was peaked with a Tl point source by centering a full-width half maximal window (25%) over the photo peak of the mercury x-rays (approximately 80 KeV). Myocardial images (200,000 counts in dogs, and 400,000 counts in human beings) were obtained as Polaroid prints and were simultaneously stored in the computer system in a 64×64 matrix[6].

The digitalized images were processed to minimize the influence of variable background on the interpretation according to the method described by Goris et al., namely interpolative background subtraction method[7,8].

The myocardial Tl uptake index was computed as a ratio of Tl activity at the various parts of the background-subtracted myocardial images to the total Tl activity injected, as shown in Fig. 1. The myocardial ROI (region of interest) for calculation of the Tl uptake index was set at various parts where the myocardium was delineated tangentially (Fig. 1). Total injected Tl activity was calculated as follows:

We used lucite phantoms of several thickness (every 0.5 cm), and each phantom had a hole, which allowed to insert injection syringe, in the middle of the full thickness.

The phantom of which thickness was equal to the thickness of the patient's (or dog's) chest was selected. Before Tl injection, the syringe containing Tl was put into the hole and counted under the scintillation camera (first counting), and after Tl injection, the remaining Tl activity in the empty syringe was again counted (second counting). Total Tl activity injected was regarded as the difference between the first and second counts.

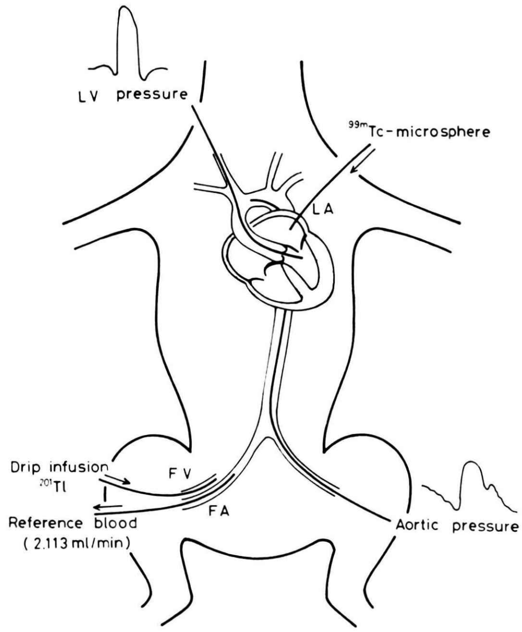

Fig. 2 Schematic illustration of animal experiments. Tl was injected via femoral vein and Tc-microsphere was injected into left atrium. Left ventricular and aortic pressure were monitored. Arterial blood sample was withdrawn form femoral artery.

Animal Studies Ten adult mongrel dogs weighing between 10 and 16 kg were anesthetized by intravenous injection of sodium pentobarbital (25–30 mg/kg). Endotracheal tubes were inserted and respirations were controlled with Harvard respirator. Heparin (250 unit/kg) iv was administered. Catheters were placed in the left ventricle and the ascending aorta retrogradely for pressure monitoring. Catheters were also placed in a femoral artery for withdrawal of a blood sample and a femoral vein for infusion of Tl (Fig. 2). A left thoracotomy was performed at the level of the fifth intercostal space. A polyvinyl catheter was inserted directly into the left atrium for administration of microsphere. In all dogs, ligations were made at various points along the left anterior descending coronary artery. The pericardium and chest wall were then closed.

Forty-five minutes after the ligation, 1 mCi of Tl was administered intravenously, and then myocardial images were obtained at the left anterior oblique position at the degree where septum was viewed perpendicular to the collimator and at the left lateral position. Then albumin microspheres (between 5×10^6 to 10×10^6 microspheres), 15 μm in diameter (9–20 μm) labeled with technecium-99m (tin reduction method) were injected into the left atrium. Simultaneously reference blood was withdrawn from the femoral artery. The left ventricular and aortic pressure were measured with Statham P23 db gauges, and ECG (limb lead 2) was monitored throughout the study.

After the completion of the study, the animal was killed with an injection of potassium chloride. The heart was excised and free wall of the right ventricle, the left atrium, great vessels, valves, surface vessels and epicardial fat were removed. Utilizing the posterior descending coronary artery as a starting point, the left ventricle was divided into four levels of eight segment each, and each was subdivided into epicardial and endocardial halves.[4] Thus the left ventricle was divided into 64 segments, and each segment was weighed, placed in plastic tube and counted in a gamma well counter. Tc and Tl activities in each myocardial segments were distinguished by measuring their half lives. Each isotope activity (count/g) was expressed as the ratio of activity in area supplied by the anterior descending coronary artery to the activity in the area supplied by the left circumflex coronary artery.

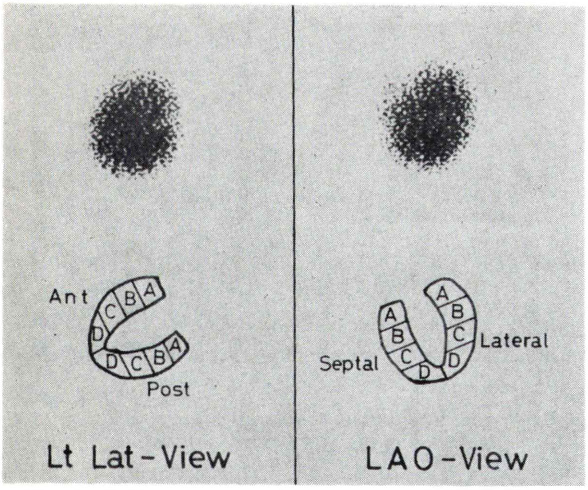

Fig. 3 ROI setting to calculate myocardial Tl uptake index in myocardial images of dogs. In left lateral image, both anterior and posterior walls were divided equally in four levels from cardiac base to apex. In left anterior oblique image, same division was made both in septal and lateral wall.

Myocardial blood flow was calculated from Tc activity of myocardium and of reference arterial blood, and reference blood flow[9].

In each dog, the Tl uptake indices were calculated at sixteen parts (eight parts in left lateral image and in left anterior oblique image respectively, as shown in Fig. 3), and they were compared with transmural Tc-microsphere distribution of the corresponding segments.

Clinical Applications (1) Exercise Stress Myocardial Imaging. Both resting and exercise stress myocardial imagings were performed in 35 patients of angiographically diagnosed coronary artery disease (50% or greater narrowing). There were 29 males and 6 females with age from 42 to 72 years. Images were recorded in the anterior, 45 degree left anterior oblique and left lateral view both in rest and in exercise stress after the intravenous injection of Tl (2 mCi). The detailed method of exercise stress perfusion imaging was described before[6,10,11].

Both Polaroid data, computer processed background-subtracted images and the Tl uptake indices were used for the interpretation.

(2) Nitroglycerin Studies. We selected ten male patients of the age of 46 to 70 who had been diagnosed angiographically as suffering from coronary artery disease (75% or greater narrowing). Radioisotope angiography (RI angiography) and Tl myocardial imaging were performed on them both before and after the sublingual administration of nitroglycerin.

At the control state, 20 mCi of Tc-99m human serum albumin was injected rapidly into right antecubital vein and ECG synchronized RI angiocardiography was obtained at 30 degrees right anterior oblique position during the first transit of radionucleide, and the observation was continued at the equilibrium state for 20 minutes. A fresh 0.6 mg nitroglycerin was then administered sublingually. Heart rate and blood pressure (cuff method) were monitored every one minute. When systolic blood pressure fell by at least 10% of control value[12], again ECG synchronized RI angiocardiography was obtained for 10 minutes.

End-diastolic and end-systolic left ventricular volume and left ventricular ejection fraction (EF), both before and after the administration of nitroglycerin, were calculated as described in detail previously[13,14].

One week after the control myocardial imaging, 0.6 mg nitroglycerin was administered sublingually, and when systolic blood pressure fell by 10% of control values, 2 mCi Tl was injected intravenously and 10 minutes later myocardial images were obtained.

Results

Animal Studies The values for hemodynamic parameters are shown in Table 1. Coronary artery ligations caused significant changes in heart rate, left ventricular peak systolic pressure and mean aortic pressure ($p<0.05$), but hemodynamic conditions remained stable from the time Tl was injected until the completion of the studies.

Percent of unbounded Tc was checked by ascending acetone methanol chromatography and it was less than five percent.

Fig. 4 (left hand) shows the relationship of myocardial Tc-microsphere distribution to the Tl concentration in one of the coronary artery ligated dogs, and they showed excellent correlation ($r=0.936$, $p<0.001$). For all dogs, the mean correlation coefficient was 0.927 ± 0.008 (range 0.915–0.936). Mean coronary blood flow in the normally perfused myocardial segments was 94.5 ± 12.0 m*l*/min/100 g of left ventricle.

Fig. 4 (right hand) shows the relationship between the myocaıdial Tc-microsphere distribution and myocardial Tl uptake index obtained by the myocardial images in one of the dogs, and they

Table 1 Values for hemodynamic parameters in dogs

	Pre-Occlusion (Mean±sd)	Occlusion at Tl inj.	Occlusion at microsphere inj.
Heart rate (/min)	136.5±7.9	155.0±6.2*	154.5±8.7*
LV systolic pressure (mmHg)	122.5±6.5	113.0±9.6*	113.8±8.5*
LV end-diastolic pressure (mmHg)	6.0±0.8	7.8±1.5	7.5±1.7
mean aortic pressure (mmHg)	102.5±8.7	90.0±10.8*	88.3±8.5*

* Significant from preocclusion control ($p<0.05$)

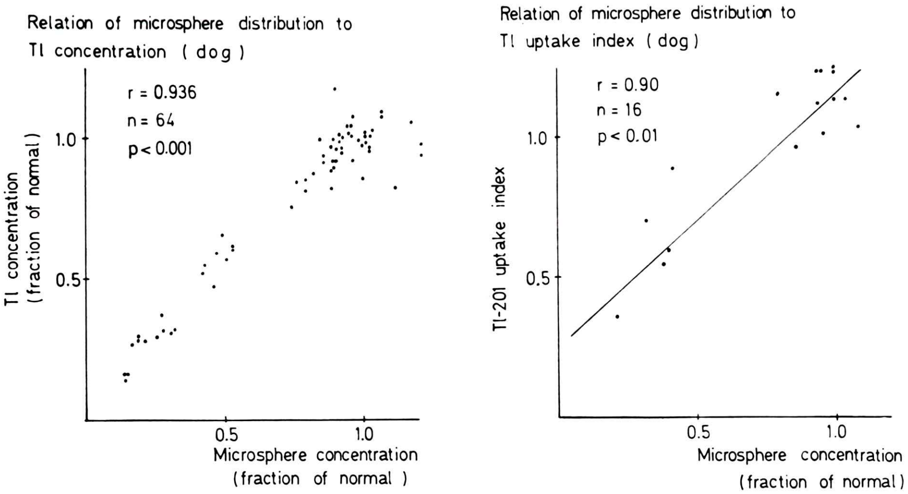

Fig. 4 Left hand: Relationship of microsphere distribution to Tl concentration in excised heart for one of dogs with coronary artery ligation. Right hand: Relationship of microsphere distribution to Tl uptake index obtained from myocardial imaging for one of dogs with coronary artery ligation.

showed also good correlation ($r=0.90$, $p<0.01$). For all dogs, mean correlation coefficient was 0.878 ± 0.014 (range 0.866–0.900).

And Tl uptake indices and myocardial Tl distribution showed good correlations, too (mean correlation coefficient: 0.890 ± 0.021).

Clinical Applications (1) Exercise Stress Myocardial Imaging. Satisfactory rest and exercise stress myocardial images were obtained in all partients studied. Out of 35 patients, exercise induced myocardial perfusion abnormality was detected in 23 patients (66%) by comparing rest and exercise stress myocardial images visually.

Fig. 5 illustrates a case of three vessel disease, in which the application of the Tl uptake index was useful for the detection of exercise induced ischemia. Rest images showed cold-spots at inferior and posterolateral segments correspond to old myocardial infarction. Exercise stress seemed to increase posterolateral perfusion as the same degree as septal segment visually. But by using the Tl uptake indices, it became evident that exercise induced hypoperfusion developed at the septal segment and there was no increase of myocardial perfusion at the posterolateral segment. In other two cases (the one had three vessel disease and the other had two vessel disease with old myocardial infarction plus 75% coronary artery stenosis), the Tl uptake indices were useful for the detection of exercise induce dischemia. Thus by using the

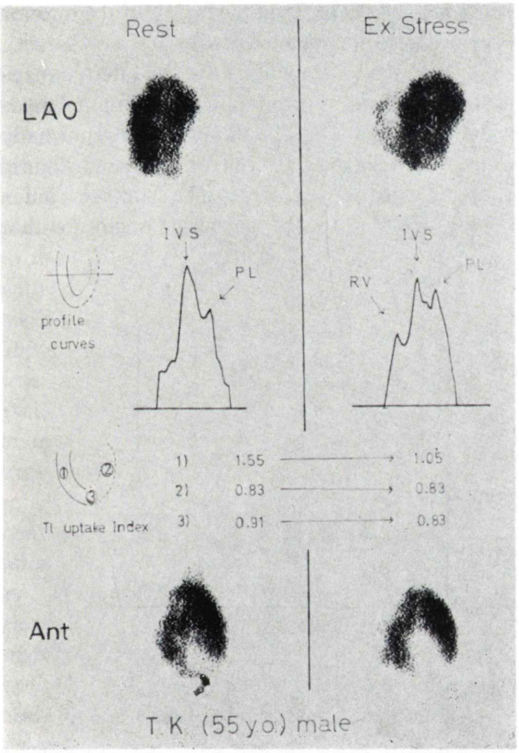

Fig. 5 Rest and exercise stress myocardial imaging in patient with three vessel disease. Rest images show cold-spots at inferior and posterolateral (PL) segment. In exercise stress, myocardial perfusion of posterolateral segment seems to be increased visually. But Tl uptake index revealed that exercise induced ischemia developed at septal segment (IVS).
abbreviations, LAO: left anterior oblique view
ANT: anterior view

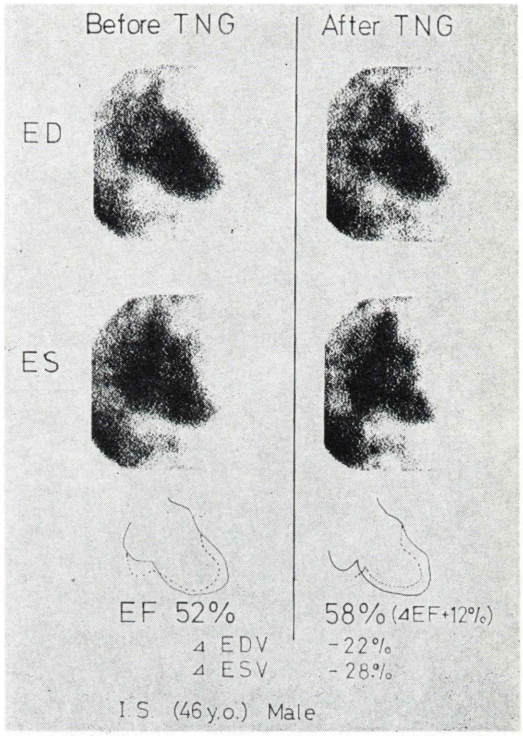

Fig. 6 RI angiocardiograms (30 degrees right anterior oblique position) in patient with right coronary artery disease before and after administration of nitroglycerin (TNG). Following agent, inferior hypokinesis was improved and EF increased from 52% to 58%.
abbreviation, ED: end-diastole, ES, end-systole
ΔEDV: percent change of EDV
ΔESV: percent change of ESV

Tl uptake indices together with myocardial images, we were able to increase diagnostic sensitivity of exercise induced ischemia up to 74% (26/35). (2) Nitroglycerin Studies. In each patient studied, RI angiography at control revealed the exsistence of one or two asynergic segments, and there were 13 asynergic segments. These asynergic segments corresponded to the hypoperfused segments at the control Tl myocardial images. Out of 13 asynergic segments, five segments (five patients) demonstrated partial improvement of wall motion abnormality with nitroglycerin, while the other eight segments (five patients) demonstrated no improvement following the agent. In five patients in whom asynergy was improved following nitroglycerin, the percent increase of EF (%ΔEF) was significant, but in five patients in whom asynergy was not improved, the percent increase of EF was slight (%ΔEF: 13.8±3.1% vs 2.0±1.1%, $p<0.01$).

Fig. 6 illustrates RI angiocardiography in a patient with right coronary artery disease, and coronary arteriogram revealed 99% stenosis of the right coronary artery at its middle part and the distal portion of the stenosis was perfused by rich collateral vessels from the left anterior descending and the left circumflex coronary artery. In this case, following the administration of nitroglycerin, hypokinesis of the inferior segment and EF was improved. Fig. 7 shows myocardial imaging before and after the administration of nitroglycerin. Following the agent, hypoperfusion of the inferior segment was improved markedly.

Fig. 8 illustrates how nitroglycerin affected myocardial perfusion in three different groups of myocardial segments. The Tl uptake indices of normally contracting segments at control decreased slightly following nitroglycerin (%ΔTl uptake index −6.85±4.90%). In the asynergic segments that

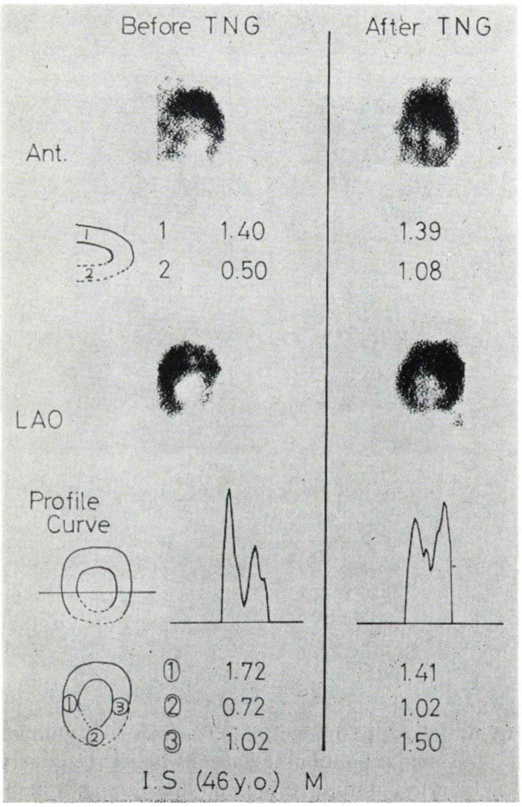

Fig. 7 Myocardial perfusion images with Tl, before and after administration of nitroglycerin in patient with right coronary artery disease whose RI angiocardiography was illustrated in FIG. 8. Following agent, inferior hypoperfusion was improved markedly.

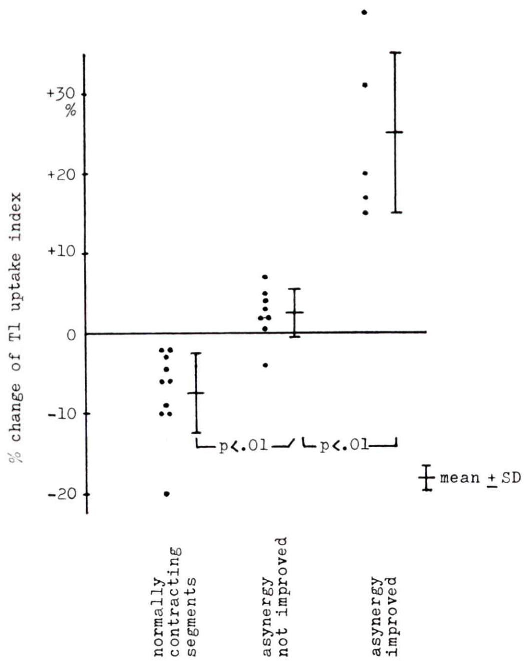

Fig. 8 Effect of nitroglycerin on myocardial perfusion (Tl uptake index) in three groups of myocardial segments.

were improved following nitroglycerin, the Tl uptake indices increased greatly (%ΔTl uptake index 25.0±11.3%), but did not increase in the asynergic segments that were not affected by nitroglycerin (%ΔTl uptake index 2.44±3.29%). In the former group, in which asynergy was improved following nitroglycerin, rich collateral vessels supplying asynergic (ischemic) segment were demonstrated, but were not in the latter group.

Discussion

Myocardial imaging with Tl offers the prospect of noninvasive assessment of regional myocardial perfusion and perfusion reserve[1,15]. Many investigators reported that regional myocardial Tl concentration reflected regional myocardial perfusion under normal and ischemic conditions in excised heart[3-5]. However these results are not extended to the myocardial imaging directly, because myocardial images are expressed as the net Tl concentration of myocardium and complicated background. So, we processed the images to minimize the influence of background activity with the interpolative background subtraction method[7,8]. Although there are some objections about this background subtraction method because true background cannot be reliably eliminated except for the tomography to obtain cross sectional images of the myocardium[16,17], our animal experiments showed that this method was superior to other method (eg simple threshold setting) in conventional myocardial imaging[8]. There are some attempts to quantitate myocardial Tl concentration as myocardial-to-background ratio[17,18]. But clearly it is not the ideal method because the myocardial-to-background ratio is influenced by both myocardial and background Tl concentration and these two factors may change in different direction or different degree by interventions employed[18]. Therefore, we made a quantitative determination of regional myocardial Tl concentration (Tl uptake index) as a ratio of Tl activity of the myocardium, where the background activity was subtracted, to total Tl activity injected. Besides, myocardial ROIs for calculation of the index were set at the parts where the myocardium was delineated tangentially in order to avoid the overlapping with contralateral myocardial wall (Fig. 1). Our animal experiments showed that the Tl uptake index reflected intramyocardial Tl concentration and regional myocardial perfusion under ischemic condition (Fig. 4, right hand).

In clinical practice, exercise stress myocardial perfusion imaging is a useful method for the detection of coronary artery disease, but the reported sensitivity was limited to around 65%[1,15]. This may be partly due to a possibility that exercise employed is not adequate to induce transient myocardial ischemia in spite of the existence of significant coronary artery stenosis. But there are several reasons that exercise induced ischemia is not detected correctly: (a) Exercise induced ischemia may be subtle in severity and/or extent to produce perfusion deficit in conventional imaging device[4]. (b) In case of patients with triple vessel disease, myocardial tracer uptake could be relatively uniformly reduced[19]. (c) In case of patients with transmural myocardial infarction plus significant coronary artery stenosis (two or three vessel disease), cold-spot due to infarction could obscure the existence induced ischemia which might develop in normally perfused area at rest. Thus, it is reasonable to consider that quantitative assessment of rest and exercise imaging would improve the diagnostic sensitivity of transient ischemia. In fact, by the Tl uptake index we were able to detect exercise induced hypoperfusion which was not detected by visual comparison of rest and exercise stress images in patients with triple vessel disease and transmural infarction plus significant coronary artery stenosis. Thus we could increase the sensitivity of the exercise stress imaging to detect coronary artery disease from 66% to 74%.

As the Tl uptake index expresses the regional perfusion change precisely, we assessed the effect of nitroglycerin on myocardial perfusion in cases with coronary artery disease. Nitroglycerin is the drug most commonly used in the treatment of ischemic heart disease, but the extent to which it relieves anginal pain by its effect on the myocardium as opposed to the systemic circulation is unclear, even though cardiac catheterization studies have been performed[20,21]. On the basis of the reaction to nitroglycerin, abnormally perfused segments (asynergic segments) at control angiocardiography were divided into two groups

(Fig. 8). The degree of its improvement by nitroglycerin seems to be dependent on the availability of collateral vessels suppling ischemic segments. Therefore, it was considered that nitroglycerin might enhance regional perfusion through collateral vessels suppling ischemic area and caused improvement of wall motion and EF. We assume that effect of nitroglycerin on myocardial perfusion in coronary heart disease might be important one as well as its effect on peripheral circulation as Cohen et al.[22] and Cohn et al[23] supposed.

In summary, we developed myocardial Tl uptake index to quantitate the regional myocardial tracer concentration, and we showed that the Tl uptake index reflected myocardial perfusion as well as myocardial Tl concentration. The applications of Tl uptake index were valuable to investigate the changes of the myocardial perfusion under several investigations.

Acknowledgment

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要　旨

^{201}Tl 心筋シンチグラフィーの定量評価
── 基礎的検討と臨床応用 ──

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^{201}Tl 心筋シンチグラフィーを定量的に評価するため，心筋局所 Tl 摂取係数を考案した．本係数は，注入総 Tl 活性に対するシンチグラムで得られた心筋像（バックグラウンド除去像）各部における Tl 活性の比で表現した．冠動脈結紮犬での実験は，Tl 摂取係数が心筋内 Tl 分布を反映しており，かつ虚血時では心筋血流分布を反映していることを示した．

冠動脈疾患35例で，運動負荷心筋シンチグラフィーを行ない，本係数を応用することでその診断率を66%から74%に上昇せしめ得た．また，冠動脈疾患10例で，ニトログリセリン投与前後に，Tl 心筋シンチ，RI 心アンギオを行ない，冠動脈疾患の心筋局所灌流に及ぼすニトログリセリンの影響に関しても検討した．

心筋 Tl 摂取係数の応用は，種々のストレス下での，心筋灌流の変化を検討する上で，有効と考えられた．

Key words: Tl uptake index, Tc-microsphere, exercise stress scintigraphy, nitroglycerin