Circ J 2002; **66:** 341 – 344

Perfusable Tissue Index Obtained by Positron Emission Tomography as a Marker of Myocardial Viability in Patients With Ischemic Ventricular Dysfunction

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In areas of severe asynergy, the clinically important task is to identify functionally recoverable myocardium. Fourteen patients with asynergy were investigated by $H_2{}^{15}O$ dynamic positron emission tomography imaging before revascularization. Regional myocardial blood flow (MBF) was determined and the water-perfusable tissue fraction (PTF) for each region of interest and the total anatomical tissue fraction (ATF) were estimated. The PTF/ATF was analyzed as the water perfusable tissue index (PTI). Asynergy was defined as segments with wall motion more than 2 SD below than that of a normal population. An increase of >0.8 SD in anterior wall segments with asynergy and an increase of >0.6 SD in inferior wall asynergy were defined as significant improvements of wall motion indicative of viable myocardium. Fifteen segments with wall motion abnormalities less than –2 SD and 10 control segments were identified; 7 segments recovered and 8 segments did not. MBF was similar in both groups of segments before revascularization (0.78±0.27 vs 0.73±0.18 $ml \cdot min^{-1} \cdot g^{-1}$, NS). The PTI in the recovered segments was significantly higher than that in the unimproved segments (0.734±0.058 vs 0.592±0.038, $p<0.0001$) and was similar to that of the control segments. After revascularization, the PTI correlated with the SD of wall motion ($p<0.05$, $r=0.58$). PTI may be a good predictor of contractile recovery after revascularization. (*Circ J* 2002; **66:** 341 – 344)

Key Words: Hibernation; Myocardial viability; Perfusable tissue index; Positron emission tomography; Ventricular dysfunction

Although many patients with multivessel coronary artery disease and severely depressed left ventricular (LV) function will benefit from revascularization, clinicians may be reluctant to recommend coronary artery bypass graft surgery (CABG) or coronary angioplasty (PTCA) in such patients without evidence of myocardial viability in the regions with severe asynergy. The clinically important tasks are to identify functionally recoverable myocardium and estimate the residual blood flow to these regions.

A number of radionuclide imaging techniques have been developed for detecting viable myocardium and the usefulness of ^{201}Tl redistribution, in particular, has been reported[1–6] as well as that of positron emission tomography (PET) using ^{13}N-ammonia and ^{18}F-2-fluoro-2-deoxyglucose (^{18}FDG)[7]. However, the true clinical value of these methods has not been well established and, moreover, these methodologies have inherent disadvantages, such prolonged examination time and/or requiring the use of radionuclides. Viable myocardium may be able to exchange water rapidly compared with necrotic tissue[8–11] and so we hypothesized that the perfusable tissue index (PTI) would identify viable myocardium and predict improved regional function after revascularization in patients with severe coronary artery disease and depressed LV function.

(Received July 18, 2001; revised manuscript received December 11, 2001; accepted January 11, 2002)

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Methods

Patients

Between February 1998 and April 2000, 14 consecutive patients (11 men, 3 women; age, 60±14 years) with chronic coronary artery disease and LV dysfunction were scheduled for coronary revascularization. The baseline LV ejection fraction was 41±13%. Six patients had diabetes mellitus. Informed consent was obtained from all 14 patients before enrollment in the study.

The patients were considered eligible for inclusion if they had the following: (1) significant stenosis of the proximal left anterior descending (LAD) coronary artery or right coronary artery (RCA) that was suitable for CABG or PTCA, (2) severe anterior or inferior wall dysfunction on contrast cineventriculography, and (3) complete revascularization of the dysfunctional segments without perioperative or periprocedural myocardial infarction defined as a new onset of Q-wave on the ECG and/or an increase in plasma cardiac enzyme activity after revascularization. The patients were documented to have high-grade stenosis (>75% diameter reduction) of either the proximal LAD or RCA by coronary angiography (CAG) and regional asynergy (severe

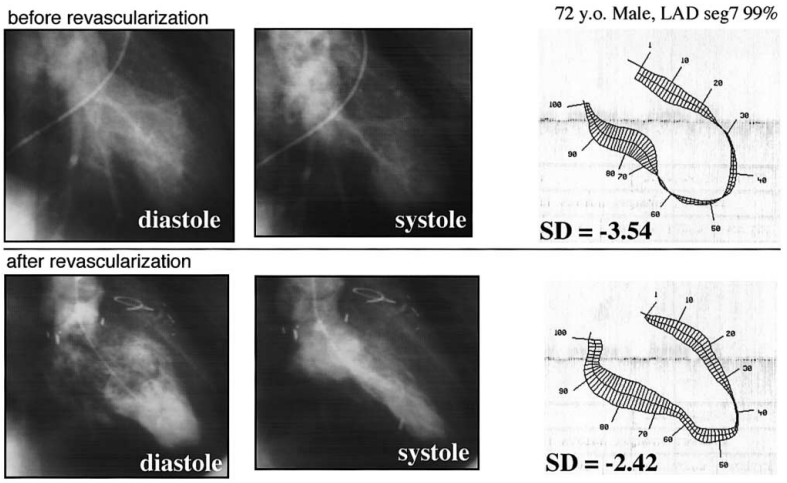

Fig 1. Regional analysis of left ventricular wall motion in a case of asynergy. In the centerline method, the SD of the LAD region was –3.54 before revascularization. The wall motion of the LAD region improved to –2.42 after revascularization.

hypokinesis, akinesis or dyskinesis) by left ventriculography (LVG). Patients with atrial fibrillation were excluded. Three patients had 1-vessel disease and 11 had 3-vessel disease. Ten patients underwent CABG and 4 had PTCA.

Cardiac Catheterization and LV Wall Motion Analysis

Initially, selective CAG and biplane LVG were performed in all patients within 1 week of the PET study and then a second round of CAG and LVG was performed 2 months after revascularization. Regional LV wall motion was analyzed and quantified by the centerline method using BILDANALYSE Cardio 500 (Kontron Instruments, Tokyo). Briefly, the left ventriculogram in the right anterior oblique projection was divided into 100 segments[12] Chords 1–9 and 81–100 were excluded from analysis because they reflect movement of the aortic root and mitral valve, respectively. The remaining chords of the LV were divided into 5 regions (anterobasal: chords 10–26; anterolateral: chords 27–43; apical: chords 44–60; inferior: chords 61–70; and posterobasal: chords 71–80). The segments of the LAD were defined as chords 10–43, and those of the RCA were defined as chords 61–80. Regional LV wall motion was expressed as the standard deviation (SD) per chord of a normal control population, and the wall motion abnormality was quantified (Fig 1). Severe asynergy was defined as a segment with an average wall motion 2 or more SD below that of a normal population. An increase of >0.8 SD in anterior wall segments with asynergy and an increase of >0.6 SD in inferior wall asynergy were defined as significant improvements of wall motion indicative of recoverable myocardium[13]

Positron Emission Tomography

Dynamic PET was performed with the Headtome IV (SET 1400) PET scanner. Oxygen-15–carbon monoxide was generated by 740–1,110 MBq (20–30 mCi) ^{15}O–water injected intravenously by an infusion pump as a slow bolus over 120 s. Beginning with tracer injection, serial emission scans were acquired in a decay–compensated mode for 6 min. Regional myocardial blood flow (MBF: $ml \cdot min^{-1} \cdot g^{-1}$) was determined, as well as the water perfusable tissue fraction (PTF) for each region of interest (ROI) (PTF: g of water perfusable tissue (PT) = PT/ml of ROI). The extravascular tissue density gives the total anatomical tissue fraction (ATF), which includes both the water perfusable and nonperfusable tissue (ATF: g of total anatomical tissue = (PT + non-PT)/ml of ROI). Thus, the ratio of PTF/ATF for a given ROI indicates the water perfusable fraction of the total tissue. We defined PTF/ATF as the water perfusable tissue index (PTI: g of PT/g of total tissue = PT + non-PT);[8–11] and we used the theory that the time–activity curves generated from ROIs placed over the left atrial chamber and LV myocardium fitted a single tissue compartment model![11,14]

Statistical Analysis

All data are expressed as the means ± SD. The 3 groups were analyzed using a one-way analysis of variance (ANOVA). When statistically significant differences were noted, group comparisons were performed using Scheffe's method. Categorical data were compared by chi-square analysis. Correlations were assessed by linear regression analysis and Pearson's correlation coefficient. Differences were considered statistically significant when $p<0.05$.

Results

Changes in LV Wall Motion on Follow-up

At baseline (as determined by LVG before revascularization), 18 segments revealed wall motion abnormalities 2 SD below normal and 10 did not. Three segments with severe asynergy did not undergo revascularization, so were excluded from analysis, leaving 15 segments to be analyzed in this study (Table 1). At follow-up, 7 of the 15 segments with severe asynergy had recovered (–3.30±0.84 to –1.75±0.63 SD) and 8 segments had not (–3.17±0.57 to –3.13±0.44 SD). There was no difference in the SD of LV wall motion between the improved and unimproved segments at baseline (–3.30±0.84 vs –3.17±0.57 SD). The proportion of patients with Q waves in the asynergic regions was not significantly different between the 2 groups (4/7 vs 3/8, NS) (Table 1).

PET Findings

The MBF estimated by ^{15}O–water in both the improved and unimproved segments was significantly lower than that in the remote segments (remote segments: 1.13±0.32, improved segments: 0.78±0.27, unimproved segments: 0.73±0.18 $ml \cdot min^{-1} \cdot g^{-1}$, respectively; Fig 2). However, there was also no difference in this index between the improved and unimproved segments. In contrast, the PTI of the improved segments did not differ from that of the remote segments, and was significantly higher than that of the unimproved segments (remote segments: 0.740±0.043, improved seg-

Table 1 Clinical, Wall Motion and PET Analysis Data

Segment no.	Site	Stenosis (%)	Q wave	pre SD	post SD	MBF ($g \cdot ml^{-1} \cdot min^{-1}$)	ATF (g/min)	PTF (g/min)	PTI
Improved									
1	LAD	75	+	–3.54	–2.42	0.70	0.642	0.474	0.738
2	RCA	75	+	–2.02	–0.64	1.07	0.577	0.427	0.740
3	LAD	99	+	–3.99	–2.10	0.72	0.708	0.597	0.843
4	LAD	95	–	–3.14	–2.14	0.48	0.764	0.544	0.712
5	RCA	100	–	–2.84	–1.78	0.83	0.766	0.514	0.671
6	RCA	95	+	–4.66	–2.01	0.45	0.612	0.466	0.761
7	RCA	95	–	–2.61	0.39	1.19	0.481	0.324	0.674
Mean		90		–3.30	–1.75	0.78	0.650	0.478	0.734
SD		10		0.84	0.63	0.27	0.104	0.088	0.058
Unimproved									
1	LAD	95	–	–3.48	–3.58	0.98	0.762	0.453	0.594
2	LAD	100	+	–3.11	–3.50	0.72	0.778	0.480	0.617
3	RCA	100	+	–3.36	–2.77	0.48	0.638	0.417	0.654
4	LAD	75	–	–2.08	–2.33	0.57	0.787	0.496	0.630
5	LAD	75	–	–3.17	–2.97	0.94	0.743	0.413	0.556
6	RCA	90	–	–3.23	–2.85	0.61	0.709	0.393	0.554
7	LAD	90	+	–3.34	–3.20	0.67	0.533	0.311	0.583
8	LAD	99	–	–4.18	–3.72	0.85	0.693	0.383	0.553
Mean		91		–3.17	–3.13	0.73	0.705	0.418	0.592
SD		10		0.57	0.44	0.18	0.085	0.059	0.038
Remote									
1	RCA	50	–	0.82	–0.82	0.58	0.682	0.565	0.828
2	RCA	90	–	0.12	1.65	1.31	0.550	0.411	0.747
3	LAD	0	–	–0.42	–0.42	1.50	0.580	0.407	0.702
4	RCA	75	–	–1.23	4.27	1.29	0.554	0.437	0.789
5	LAD	75	–	2.97	0.57	1.14	0.710	0.493	0.694
6	RCA	95	–	1.30	0.61	0.75	0.686	0.514	0.749
7	RCA	0	–	–0.14	–0.09	0.93	0.648	0.460	0.710
8	LAD	90	–	–1.40	–0.62	1.56	0.633	0.447	0.706
9	RCA	0	–	–1.61	–0.43	1.19	0.592	0.445	0.752
10	RCA	90	–	–1.83	–1.00	0.55	0.781	0.561	0.718
Mean		47		0.04	0.52	1.13	0.642	0.474	0.740
SD		42		1.47	1.60	0.32	0.075	0.057	0.043

RCA, right coronary artery; LAD, left anterior descending coronary artery; pre SD, standard deviation of regional wall motion before revascularization; post SD, standard deviation of regional wall motion after revascularization; MBF, myocardial blood flow; ATF, anatomical tissue fraction; PTF, perfusable tissue fraction; PTI, perfusable tissue index.

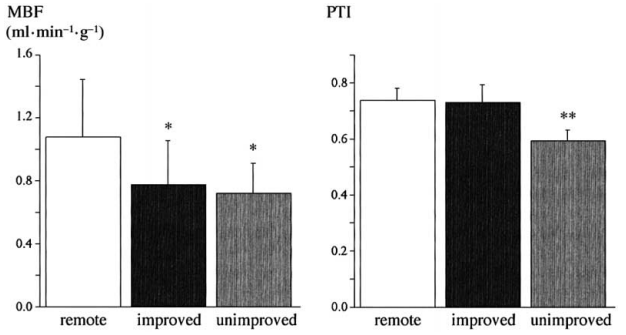

Fig 2. Myocardial blood flow (MBF) and perfusable tissue index (PTI) before revascularization. MBF was similar in both the improved and unimproved segments (0.780±0.276 vs 0.731±0.180 $ml \cdot min^{-1} \cdot g^{-1}$, respectively). In contrast, PTI was significantly higher in the improved segments than in the unimproved segments (0.734±0.058 vs 0.592±0.038, respectively), and was similar to the control (remote) segments. *p<0.05 vs remote, **p<0.0001 vs remote and improved.

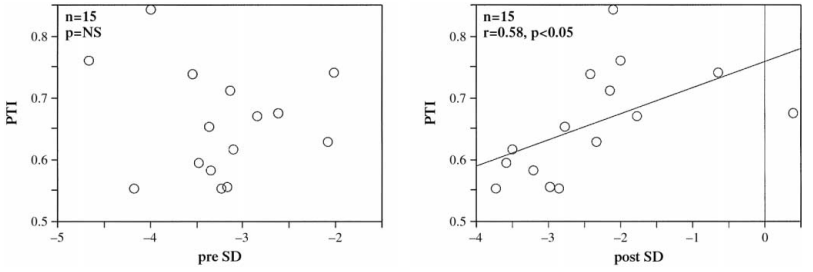

Fig 3. Correlation between LV wall motion and perfusable tissue index (PTI). In the segments with severe LV dysfunction, the PTIs significantly correlated with the SD of LV wall motion after revascularization, but not before revascularization.

ments: 0.734±0.058, unimproved segments: 0.592±0.038, respectively). In the 15 segments with severe LV dysfunction, the PTI significantly correlated with the SD of LV wall motion after revascularization but not before (Fig 3).

Discussion

Because many patients with multivessel coronary artery disease and severe LV dysfunction will benefit from revascularization, it is very important to precisely identify recoverable myocardium and a number of radionuclide imaging techniques have been developed for this purpose. Schwaiger et al[16] and Tillisch et al[17] identified viable myocardium by demonstrating sustained glucose utilization in hypoperfused asynergic segments using ^{13}N-ammonia and ^{18}FDG to qualitatively assess MBF and residual tissue metabolism, respectively. However, the uptake of ^{18}FDG is influenced by the patient's metabolic state, which can be affected by diseases such as diabetes mellitus and by plasma glucose levels.

In the present study, we demonstrated that the PTI can identify viable myocardium and predict improvement in regional function after revascularization in patients with depressed LV function. This method is based on the hypothesis that only viable myocardium exchanges water rapidly, so, in theory, the PTI should differentiate hibernating myocytes from necrotic ones in regions of myocardial infarction[9] Iida et al reported that the absolute mass and proportion of histochemically defined noninfarcted tissue could be quantitated with PTF and PTI in the canine heart with an old myocardial infarction[18] In our study, the PTI correlated with wall motion after revascularization, but not before. Although the relationship between the degree of myocardial necrosis and subsequent improvement of myocardial contractility after revascularization can be guessed, the precise details of this relationship should be obvious. de Silva et al reported that contractile recovery occurred only in segments where the PTI was ≥0.7, and there was good agreement between the PTI and FDG methods for predicting improvements in regional wall motion after revascularization[10] Our results agree with that previous report.

Dobutamine echocardiography is the predominant imaging method used to assess viable but dysfunctional myocardium to predict early improvement in regional LV function after PTCA[19,20] and future studies need to compare PTI and dobutamine echocardiography as the most useful predictor of viable myocardium.

Study Limitations

First, only a small number of patients with severe ischemic LV dysfunction were evaluated. Second, the follow-up period was short, and long-term follow-up is required. Third, the study group included many patients with 3-vessel disease. Therefore, the differences in the evaluations of the control and unimproved segments to those of de Silva et al might reflect the differences in the patients' characteristics (de Silva and present study: 0.97 and 0.74, 0.45 and 0.59, respectively).

Acknowledgments

This work was presented in part at the 65th Annual scientific Meeting of the Japanese Circulation Society, Kyoto, March 2001.

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