J Cardiol 1996; 28: 17–25

Delayed Metabolic Recovery of Hibernating Myocardium After Percutaneous Transluminal Coronary Angioplasty : Assessment With Iodine-123-Betamethyl-p-Iodophenyl-Pentadecanoic Acid Imaging

Yasuchika TAKEISHI, MD
Hiroyuki ATSUMI, MD
Satomi FUJIWARA, MD
Hitonobu TOMOIKE, MD

Abstract

The time course of improvement in fatty acid metabolism after percutaneous transluminal coronary angioplasty (PTCA) was investigated using echocardiography and fatty acid metabolic imaging with iodine-123-betamethyl-*p*-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) before, 1 week and 3 months after PTCA in 31 patients with angina pectoris.

Decreased left ventricular wall motion before PTCA improved 1 week after PTCA in 13 of 31 patients. ^{123}I-BMIPP uptake was reduced in these 13 patients before PTCA, and did not improve 1 week after PTCA. Decreased myocardial uptake of ^{123}I-BMIPP improved 1 week after PTCA in eight of 23 patients (group A). Thirteen patients in whom ^{123}I-BMIPP uptake had not improved 1 week after PTCA showed a delayed recovery of 3 months after PTCA (group B). All patients in groups A and B showed improvement in wall motion 1 week after PTCA. Patients in group B had a higher incidence of unstable angina (77% vs 25%, $p<0.01$), 99% or 100% stenosis (62% vs 13%, $p<0.01$) and collateral vessels (46% vs 13%, $p<0.05$) than those in group A.

Serial fatty acid metabolic imaging with ^{123}I-BMIPP after PTCA showed delayed metabolic recovery after improvement in wall motion in 13 of 23 patients. The presence of severe myocardial ischemia before PTCA enhanced the chronological discrepancies between the recovery of wall motion and fatty acid metabolism.

Key Words

Coronary artery disease, Radionuclide imaging, Metabolism, Myocardium (hibernating), Angioplasty (coronary)

INTRODUCTION

Fatty acids provide more than 70% of myocardial energy requirements at rest under normal aerobic conditions[1]. Positron emission tomography with carbon-11 palmitate has been used for the evaluation of myocardial fatty acid metabolism[2,3]. For practical purposes, single photon radionuclides that can assess myocardial metabolism have long been desired[4–8]. Recently, iodine-123-betamethyl-*p*-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) has been developed and used as a tracer for myocardial fatty acid metabolism[9,10].

When myocardial perfusion is chronically reduced but is still sufficient to maintain the viability of the tissue, myocardial function remains impaired

山形大学医学部 第一内科：〒990–23 山形市飯田西 2–2–2
The First Department of Internal Medicine, Yamagata University School of Medicine, Yamagata
Address for reprints: TAKEISHI, Y, MD, The First Department of Internal Medicine, Yamagata University School of Medicine, Iida-nishi 2–2–2, Yamagata 990–23
Manuscript received April 3, 1996; revised May 20, 1996; accepted May 21, 1996

Selected abbreviations and acronyms

^{123}I-BMIPP = iodine-123-betamethyl-*p*-iodophenyl-pentadecanoic acid
PTCA = percutaneous transluminal coronary angioplasty
Tc = technetium

for as long as myocardial perfusion is inadequate[11]. Myocardium in this condition is referred to as hibernating[11,12]. Because hibernating myocardium is metabolically viable tissue, decreased wall motion can improve after restoration of coronary blood flow[13–15]. However, the timing of metabolic recovery following reestablishment of perfusion is only partially understood. The relationship between the improvement in perfusion, wall motion and metabolism has not been rigorously examined.

The present study investigated the time course of the improvement in wall motion and fatty acid metabolism of the ischemic myocardium after restoration of coronary blood flow. Left ventricular wall motion was sequentially examined by echocardiography and myocardial fatty acid metabolism by ^{123}I-BMIPP before, 1 week and 3 months after percutaneous transluminal coronary angioplasty (PTCA) in patients with angina pectoris.

MATERIALS AND METHODS

Subjects and study protocol

Thirty-one patients with angina pectoris who received successful PTCA were studied. The exclusion criteria consisted of a history of myocardial infarction, previous PTCA or coronary artery bypass grafting, and evidence of coronary restenosis after PTCA. There were 21 males and 10 females with a mean age of 69 years. Myocardial fatty acid metabolic imaging with ^{123}I-BMIPP and echocardiography were obtained before, 1 week and 3 months after PTCA. The present study was performed after written informed consent was obtained.

Myocardial metabolic imaging with ^{123}I-BMIPP

Data acquisition and processing : Myocardial single photon emission computed tomography was performed in all patients as previously described[16]. Briefly, after an overnight fast, a dose of 148 MBq of ^{123}I-BMIPP was injected intravenously in the resting supine position. Data acquisition was carried out 20 min after the ^{123}I-BMIPP administration. All studies were obtained on a large field-of-view rotating gamma camera (SIEMENS, ZLC-7500 DIGITRAC) equipped with a parallel-hole, high-resolution collimator. Energy discrimination was provided by a 20% window centered at 159 keV. Thirty-two images were obtained over a 180-degree arc from the 30-degree right anterior oblique to the 60-degree left posterior oblique positions. Each image was accumulated for 50 sec. The data were stored on a 64×64 matrix. Data processing was performed on a nuclear medicine computer system (SHIMADZU, SCINTIPAC-700). A series of contiguous transaxial images of 6 mm thickness were reconstructed by a filtered back-projection algorithm without attenuation correction. These transaxial images were then reoriented in the short axis, vertical long axis, and horizontal long axis of the left ventricle.

Image interpretation : The myocardial distribution of ^{123}I-BMIPP was analyzed in the three standard orthogonal tomographic imaging planes as follows : the anterior, septal, inferior, and lateral regions in the short-axis view; the anterior, apical, and inferior regions in the vertical long-axis view; and the septal, apical, and lateral regions in the horizontal long-axis view. The left ventricle was divided into nine segments by splitting the anterior, septal, inferior, and lateral walls into basal and apical segments, including an extra segment for the apex[17]. The image was interpreted by two independent observers who were unaware of the clinical history and angiographic findings of the patients. A 5-point scoring system was used for evaluating the regional myocardial uptakes of the tracer as described previously[18] : 0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced, and 4 = no activity. The grading was settled by consensus between the two observers. When they disagreed on the results, a third observer reviewed the images, and his judgment was accepted. An improvement in ^{123}I-BMIPP uptake after PTCA was defined as a decrease of more than one in the segmental score.

Echocardiography

Two-dimensional echocardiography was performed before, 1 week and 3 months after PTCA for the assessment of left ventricular wall motion by an

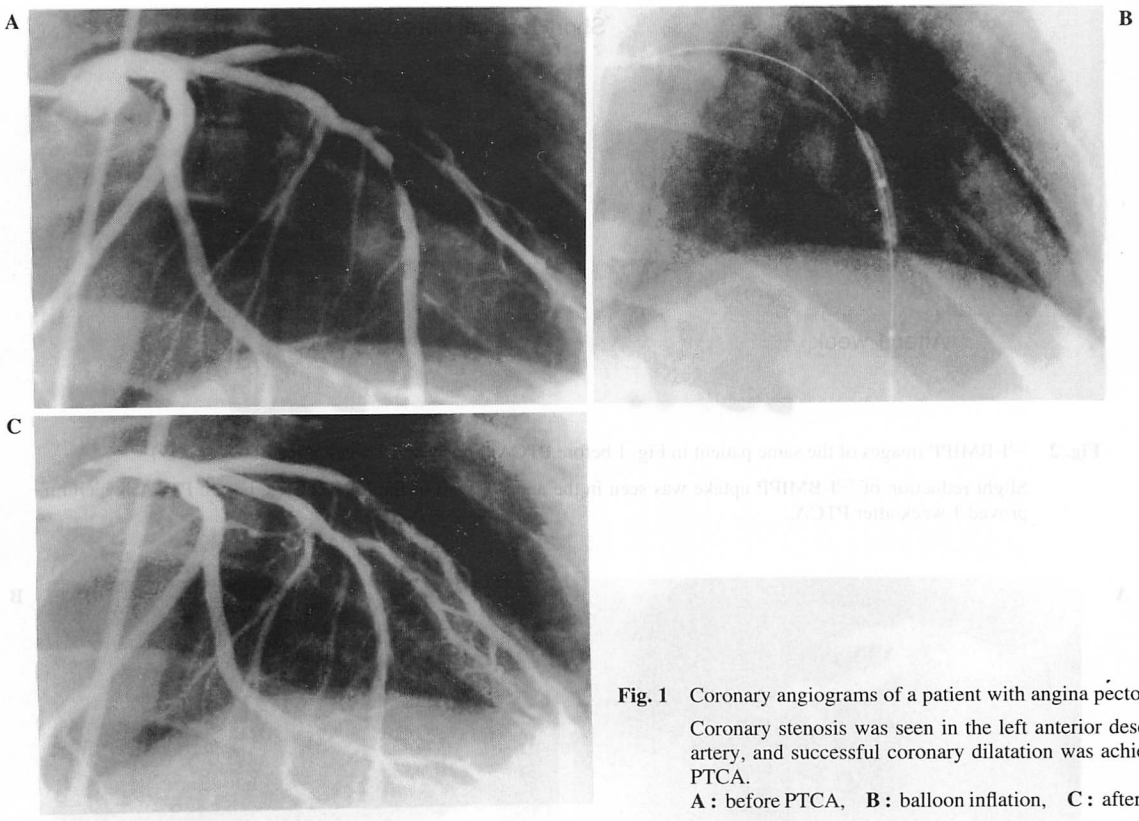

Fig. 1 Coronary angiograms of a patient with angina pectoris
Coronary stenosis was seen in the left anterior descending artery, and successful coronary dilatation was achieved by PTCA.
A: before PTCA, **B**: balloon inflation, **C**: after PTCA.

experienced cardiologist. Standard parasternal short- and long-axis views and an apical four-chamber view were recorded on videotapes. The echocardiograms were analyzed on a CRT (cathode-ray tube) by two independent observers who had no knowledge of the patients' clinical data. The left ventricle was divided into five segments in each view, and the level of segmental wall motion was scored as follows[18]: 0=normal, 1=mild hypokinesis, 2=moderate hypokinesis, 3=akinesis, 4=dyskinesis. The improvement in regional wall motion after PTCA was defined as a decrease of more than one in the segmental wall motion score. Inadequately visualized segments were excluded in the present study. When the first two observers did not agree, the judgment of the third investigator was accepted.

Statistics

Data are reported as mean ±standard deviation. Continuous variables were compared by Student's *t*-test, and the differences in proportion (categorical variables) were examined by χ^2 test. A p value$<$ 0.05 was considered significant.

RESULTS

Case presentation

Fig. 1 shows the coronary angiograms of a 60-year-old male patient with effort angina pectoris. Coronary stenosis of 90% was observed in the left anterior descending artery. Successful coronary dilatation was obtained by PTCA. **Fig. 2** shows the myocardial ^{123}I-BMIPP images of this patient. Myocardial ^{123}I-BMIPP accumulation was slightly decreased in the anterior wall of the left ventricle before PTCA. One week after PTCA, ^{123}I-BMIPP uptakes were normalized.

Fig. 3 shows coronary angiograms of a 70-year-old male patient with unstable angina (worsening effort angina). The left anterior descending artery was occluded, and successful coronary reflow was achieved by PTCA. **Fig. 4** shows myocardial ^{123}I-BMIPP images of this patient. Before PTCA, decreased uptakes of ^{123}I-BMIPP were seen in the anterior, septal and apical regions of the left ventricle, which were unchanged 1 week after PTCA. The reduced uptake of ^{123}I-BMIPP improved 3 months after PTCA.

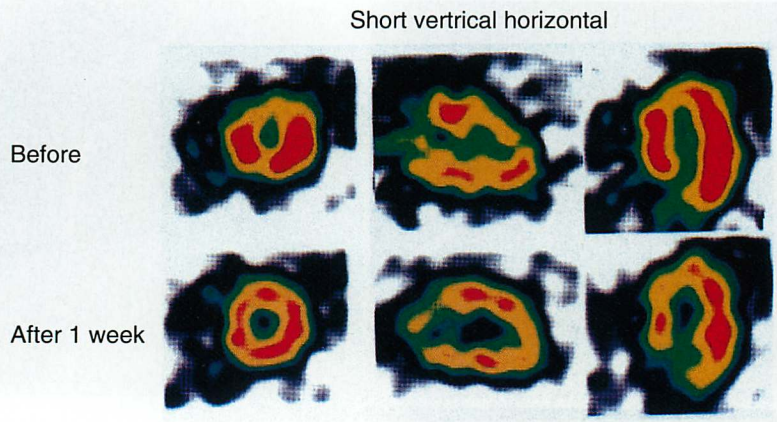

Fig. 2 ^{123}I-BMIPP images of the same patient in Fig. 1 before PTCA (*upper*) and 1 week after PTCA (*lower*)

Slight reduction of ^{123}I-BMIPP uptake was seen in the anterior wall of the left ventricle before PTCA, which improved 1 week after PTCA.

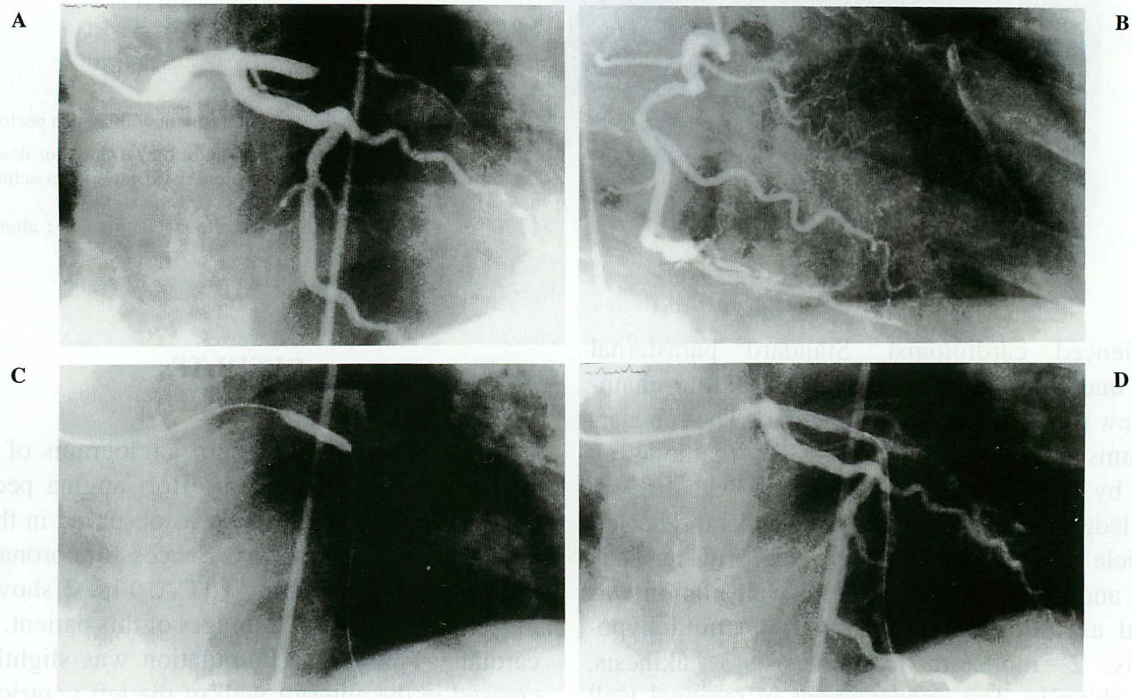

Fig. 3 Coronary angiograms of a patient with unstable angina

The left anterior descending artery was occluded, and well-developed collateral vessels were seen from the right coronary artery. Successful coronary reflow was achieved by PTCA.

A : left coronary artery before PTCA, **B :** right coronary artery before PTCA, **C :** balloon inflation, **D :** after PTCA.

Changes in wall motion and fatty acid metabolism after PTCA

Before PTCA, 14 patients had decreased left ventricular wall motion (**Fig. 5**), and 17 patients had normal wall motion. One week after PTCA, 13 of 14 patients with decreased wall motion showed improvement in wall motion. In one patient who had not improved 1 week after PTCA, left ventricular wall motion improved 3 months after PTCA. Worsening of wall motion was observed in one patient. Acute coronary dissection occurred during the PTCA procedure, and the level of serum creatine kinase was increased after PTCA in this patient.

Changes in myocardial ^{123}I-BMIPP uptake after PTCA are shown in **Fig. 6**. Before PTCA, myocardial accumulation of ^{123}I-BMIPP was decreased in

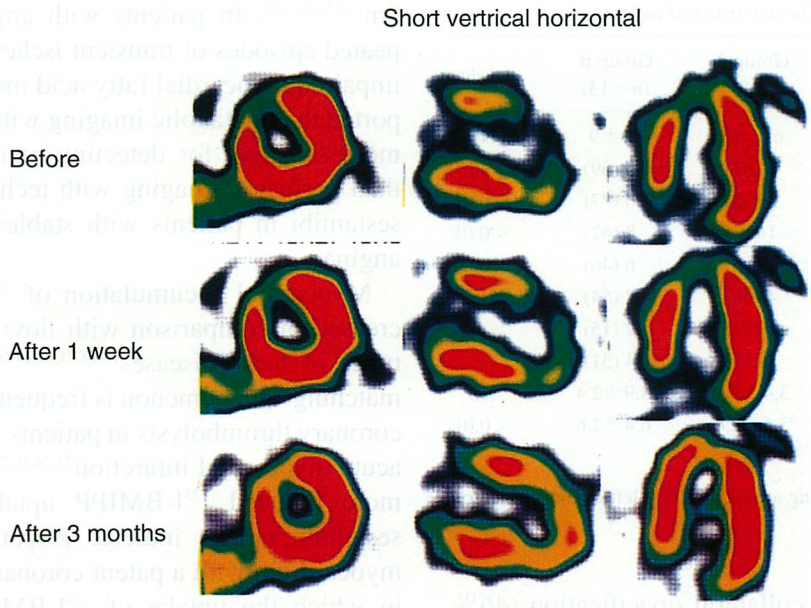

Fig. 4 Myocardial ^{123}I-BMIPP images of the same patient in Fig. 3 before (*upper*), 1 week after (*middle*), and 3 months after (*lower*) PTCA

Myocardial uptakes of ^{123}I-BMIPP were reduced in the anterior, septal and apical wall of the left ventricle, and were unchanged 1 week after PTCA. Myocardial uptakes of ^{123}I-BMIPP had improved 3 months after PTCA.

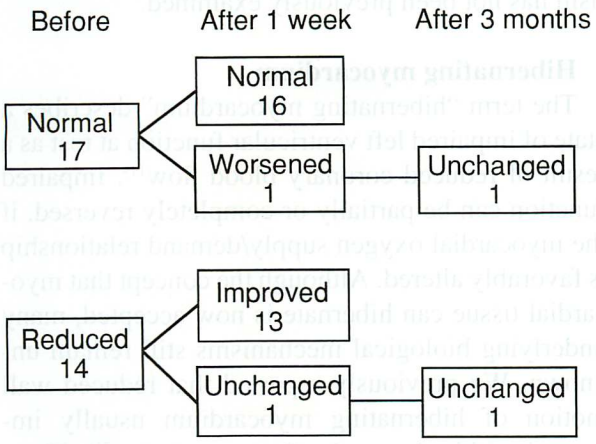

Fig. 5 Changes in left ventricular wall motion after PTCA

Out of 14 patients with decreased wall motion before PTCA, 13 patients showed improvement in wall motion 1 week after PTCA.

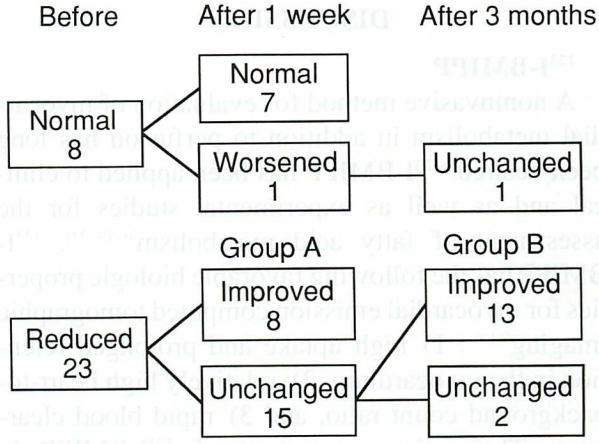

Fig. 6 Changes in ^{123}I-BMIPP uptake after PTCA

Among 23 patients with decreased uptake of ^{123}I-BMIPP before PTCA, myocardial uptake of ^{123}I-BMIPP improved in eight patients 1 week after PTCA. Out of 15 patients who had not improved 1 week after PTCA, 13 patients showed delayed recovery of ^{123}I-BMIPP uptake 3 months after PTCA.

23 patients. Out of 23 patients, eight patients (group A) showed an improvement in ^{123}I-BMIPP uptake 1 week after PTCA. Out of 15 patients who had not improved 1 week after PTCA, 13 patients (group B) showed delayed recovery of ^{123}I-BMIPP uptake 3 months after PTCA. Left ventricular wall motion improved 1 week after PTCA in all patients of both groups A and B. Myocardial ^{123}I-BMIPP uptake did not show any improvement after PTCA in two patients. Worsening of ^{123}I-BMIPP uptake was observed in one patient who showed an increase of serum creatine kinase level due to coronary dissection.

Clinical features, angiographic and scintigraphic results were compared between groups A and B (**Table 1**). Age, sex, the site of PTCA, and asynergy score before PTCA showed no differences. The incidence of unstable angina (77% vs 25%, $p<0.01$), critical coronary stenosis of 99% or 100% (62% vs

Table 1 Characteristics of patients

	Group A (n=8)	Group B (n=13)	p value
Age (yr)	67±11	70±9	NS
Sex (male)	5 (63)	9 (69)	NS
Unstable angina	2 (25)	10 (77)	<0.01
99% or 100% stenosis	1 (13)	8 (62)	<0.01
Collateral opacification	1 (13)	6 (46)	<0.05
PTCA site LAD	4 (50)	7 (54)	NS
LCX	1 (13)	2 (15)	
RCA	3 (37)	4 (31)	
Asynergy score	3.4±2.1	3.9±2.4	NS
^{123}I-BMIPP defect score	3.6±2.4	6.4±2.6	<0.01

( ): %.
LAD=left anterior descending artery; LCX=left circumflex artery; RCA=right coronary artery.

13%, $p<0.01$), and collateral opacification (46% vs 13%, $p<0.05$) were higher in group B than in group A. Defect scores of ^{123}I-BMIPP before PTCA were lower in group A than in group B (3.6±2.4 vs 6.4±2.6, $p<0.01$).

DISCUSSION

^{123}I-BMIPP

A noninvasive method for evaluation of myocardial metabolism in addition to perfusion has long been desired. ^{123}I-BMIPP has been applied to clinical and as well as experimental studies for the assessment of fatty acid metabolism[16,19–22]. ^{123}I-BMIPP has the following favorable biologic properties for myocardial emission computed tomographic imaging[9,10]: 1) high uptake and prolonged retention in the myocardium, 2) relatively high heart-to-background count ratio, and 3) rapid blood clearance. The major component of ^{123}I-BMIPP in myocytes may be the triglyceride pool, and ^{123}I-BMIPP is partially metabolized, firstly by alpha-oxidation followed by beta-oxidation. Although ^{123}I-BMIPP is not an ideal tracer for myocardial fatty acid metabolism, the myocardial accumulation of ^{123}I-BMIPP is associated with triglyceride synthesis, which in part reflects fatty acid utilization[23]. Myocardial imaging with ^{123}I-BMIPP can provide additional information for myocardial perfusion imaging. The safety and potential usefulness of this isotope have now been confirmed in clinical trials[24–28].

Extensive reports have shown that fatty acid metabolism is altered in the ischemic myocardium[2–8,18,21–30]. In patients with angina pectoris, repeated episodes of transient ischemia may result in impaired myocardial fatty acid metabolism. We reported that metabolic imaging with ^{123}I-BMIPP was more sensitive for detecting myocardial ischemia than perfusion imaging with technetium (Tc)-99m sestamibi in patients with stable[30] and unstable[18] angina.

Myocardial accumulation of ^{123}I-BMIPP is decreased in comparison with flow tracer in various types of heart diseases[16,18,21,22,24,26,27,30]. This "mismatching" phenomenon is frequently observed after coronary thrombolysis in patients with acute or subacute myocardial infarction[21,24,26,27]. Segments with more reduced ^{123}I-BMIPP uptake than Tc-99m sestamibi uptake indicate jeopardized but viable myocardium with a patent coronary artery[26]. Areas in which the uptake of ^{123}I-BMIPP is more decreased than that of Tc-99m sestamibi might be due to a delayed recovery of fatty acid metabolism after reperfusion. However, serial ^{123}I-BMIPP imaging to confirm the delayed recovery of fatty acid metabolism has not been previously examined.

Hibernating myocardium

The term "hibernating myocardium" describes a state of impaired left ventricular function at rest as a result of reduced coronary blood flow[11]. Impaired function can be partially or completely reversed, if the myocardial oxygen supply/demand relationship is favorably altered. Although the concept that myocardial tissue can hibernate is now accepted, many underlying biological mechanisms still remain unknown. We previously reported that reduced wall motion of hibernating myocardium usually improved within 1 month after reperfusion[31]. However, the timing of metabolic recovery following the reestablishment of perfusion is only partially understood, and the relationship between the recovery of wall motion and metabolism has not been rigorously examined. In the present study, myocardial ^{123}I-BMIPP uptake improved 1 week after PTCA in eight of 23 patients (group A). Metabolic recovery was concordant with the improvement in perfusion and wall motion in these patients. In 13 patients (group B), ^{123}I-BMIPP uptake did not improve 1 week after PTCA, although wall motion had improved. ^{123}I-BMIPP uptake improved 3 months after PTCA. Metabolic recovery was delayed after improvements in perfusion and wall motion in these

patients.

We then tried to clarify the characteristics of patients who showed delayed metabolic recovery. The incidence of unstable angina, 99% or 100% stenosis, and collateral vessels were more frequently observed in patients of group B than in those of group A. Defect scores of ^{123}I-BMIPP were lower in group A than in group B. Such evidence indicates that myocardial ischemia before PTCA is more severe in patients with delayed metabolic recovery.

Limitations of the study

We examined ^{123}I-BMIPP imaging and echocardiography before, 1 week and 3 months after PTCA. Repeated evaluation of ^{123}I-BMIPP imaging is required to more clearly define the time course of metabolic recovery. Myocardial uptake of ^{123}I-BMIPP did not improve 3 months after PTCA in two patients. Because successful coronary dilatation has been maintained for 3 months after PTCA in these patients, follow-up ^{123}I-BMIPP imaging should again be performed.

CONCLUSIONS

Serial fatty acid metabolic imaging with ^{123}I-BMIPP after PTCA showed that metabolic recovery was delayed after improvement in a wall motion. Therefore, abnormal ^{123}I-BMIPP images soon after PTCA did not necessarily reflect irreversible damage to fatty acid metabolism. The presence of severe myocardial ischemia before PTCA enhanced the chronological discrepancies between the recovery of wall motion and fatty acid metabolism.

要　約

PTCA 後の心筋脂肪酸代謝の回復：^{123}I-BMIPP による検討

竹石　恭知　　熱海　裕之　　藤原　里美　　友池　仁暢

梗塞のない虚血心筋における PTCA 後の心筋脂肪酸代謝と左室壁運動の回復過程を明らかにし，また代謝と壁運動の両者における回復過程の違いに関連する因子を検討した．

PTCA を施行した 31 例を対象とした．いずれも初回 PTCA である．心筋梗塞の既往はなく，また 3 ヵ月後の冠動脈造影で再狭窄を認めていない．PTCA 前と PTCA 1 週後および 3 ヵ月後に ^{123}I-BMIPP と心エコー図検査を行い，心筋脂肪酸代謝と左室壁運動を経時的に評価した．^{123}I-BMIPP の心筋集積は，9 分節について 5 段階の defect score (0：正常–4：集積なし) を用いて判定した．壁運動は 5 段階の asynergy score (0：正常–4：dyskinesis) により評価した．^{123}I-BMIPP，壁運動ともに，PTCA 後 score が 1 以上低下した場合を改善ありと判定した．

PTCA 前，14 例に壁運動の低下を認め，うち 13 例は PTCA 1 週後に壁運動の改善をみた．この 13 例では PTCA 前，^{123}I-BMIPP 集積は全例で低下しており，PTCA 1 週後では改善を認めなかった．PTCA 前に ^{123}I-BMIPP の集積低下を認めた 23 例中 8 例 (A 群) は，PTCA 後 1 週で血流の改善に伴い ^{123}I-BMIPP 集積，左室壁運動ともに改善した．13 例 (B 群) は壁運動のみ PTCA 後 1 週で改善し，^{123}I-BMIPP 集積の改善は 3 ヵ月以降まで遷延した．A 群と B 群で臨床像，冠動脈造影，心エコー図，^{123}I-BMIPP 所見を比較した．B 群は A 群よりも，PTCA 前の不安定狭心症 (77% vs 25%, $p<0.01$) および冠動脈の完全ないし亜完全閉塞 (62% vs 13%, $p<0.01$) の頻度が高く，PTCA 前の ^{123}I-BMIPP の集積は低下していた (6.4±2.6 vs 3.6±2.4, $p<0.01$)．

PTCA 後の心筋脂肪酸代謝と左室壁運動の回復過程に時間的乖離を認め，PTCA 前の心筋虚血の重症度の関与が示唆された．

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