An Effective Tool to Detect Lesions Causing Unstable Angina With Multivessel Disease: Iodine-123-Betamethyl-p-Iodophenyl-Pentadecanoic Acid Single Photon Emission Computed Tomography

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Abstract

Radiolabeled fatty acids such as iodine-123-betamethyl-p-iodophenyl-pentadecanoic acid (BMIPP) have unique metabolic properties suggesting potential use as myocardial perfusion tracers.

The uptakes of BMIPP and thallium 201 were compared using single photon emission computed tomography (SPECT) in 24 patients displaying unstable angina with multivessel disease at a mean of 3.4 days after admission. Coronary angiography was performed within a week. Uptake was considered normal if the activity was greater than 80% of the normal area, mildly reduced if 50% to 79%, and severely reduced if less than 50%. The regional activities in four quadrants in short-axis slices were measured from basal, mid and apical sets. We attempted to identify the causative lesion on dual SPECT imaging. We planned the following management of each patient based on the results of the dual SPECT study.

BMIPP activity imaging found 4 segments (1.4%) with severe decrease, 70 (24.3%) with mild decrease, and 214 (74.3%) with normal uptake. In contrast, Tl activity imaging showed normal uptake in 68 of 74 abnormal BMIPP activity segments. Furthermore, all segments with abnormal BMIPP uptake were matched with locations of coronary artery stenosis by coronary angiography. Accordingly, coronary revascularization (percutaneous transluminal coronary angioplasty, coronary artery bypass grafting) was performed based on BMIPP SPECT.

Reductions in BMIPP activity were common in patients with unstable angina with multivessel disease. BMIPP SPECT is an excellent tool for detecting the causative lesion in unstable angina. The subsequent intervention could be performed with less risk based on the strategy of dilating the only causative lesion which was detected by the BMIPP SPECT in patients with multivessel disease displaying unstable angina.

Key Words

Fatty acids, Unstable angina, Radioisotopes, Coronary artery disease

INTRODUCTION

Fatty acids are the primary energy source for the myocardium, but their oxidation is easily impaired

under various conditions. Various efforts have been made to label fatty acid compounds to probe regional fatty acid metabolism *in vivo*. Structurally modified fatty acids that reveal normal myocardial

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extraction but are not readily catabolized through the oxidative chain can be used to evaluate regional fatty acid uptake, since they should not be catabolized and should thus expose prolonged myocardial retention.

Goodman et al. 1) investigated the use of methyl branching in position 3 of the alkanoic acid chain of terminal iodophenyl fatty acids to inhibit β -oxidation and prolonged myocardial retention. The effect of methyl branching at the position 3 on myocardial retention in rats was assessed by a comparison of the distribution of the methyl-branched agent with myocardial uptake of the corresponding straight chain analogue, iodine-125 iodophenyl-pentadecanoic acid (IPPA). The increased myocardial uptake and retention of radioactivity following injection of iodine-123-betamethyl-p-iodophenyl-pentadecanoic acid (BMIPP), in comparison with IPPA, suggested that methyl branching at position 3 could be an effective means of inhibiting myocardial metabolism. BMIPP shows longer myocardial retention in rats than the straight chain IPPA analogue, but not irreversible retention. Accordingly, it was suggested that BMIPP would have a good clinical application in myocardial image tracing. Some investigators reported that imaging of BMIPP uptake and retention after injection indicates the presence of metabolic abnormality in the myocardium²⁻⁴). Recent clinical studies indicate that discrepancies in the activities between BMIPP and thallium 201 (Tl) are often demonstrated in patients suffering from ischemic heart disease⁵⁻⁷⁾.

Unstable angina is also clinically important, not only due to its frightening and disabling nature but also due to the distinct possibility that it could lead to an acute myocardial infarction^{8,9)}. Accordingly, unstable angina pectoris is a serious and potentially dangerous condition, and management of the causative lesion must be approached with this in mind.

We have frequently found that BMIPP imaging shows a reduction of activity in patients with unstable angina. Our present study was undertaken to investigate the clinical implication of BMIPP single photon emission computed tomography (SPECT) to manage patients displaying unstable angina with multivessel disease.

MATERIALS AND METHODS

Patient selection

This study included 24 consecutive patients pre-

Selected abbreviations and acronyms

BMIPP=iodine-123-betamethyl-p-iodophenyl-pentadecanoic

CABG = coronary artery bypass grafting

FDG = fluoro-deoxyglucose

IPPA = iodine-125 iodophenyl-pentadecanoic acid

LAD=left anterior descending artery

LCX = left circumflex coronary artery

RCA = right coronary artery

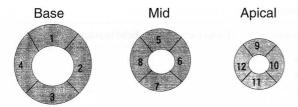
SPECT = single photon emission computed tomography

Tl=thallium

senting with unstable angina with multivessel disease from December 1993 through December 1994. Patients with transmural previous infarction were excluded. During this period, 46 patients were admitted to the coronary care unit with demonstrated unstable angina. All patients had severe ischemic symptoms (Canadian angina class III and IV) despite medical therapy. All had reversible electrocardiogram changes of ischemia recorded at rest. All patients were placed into the class II-B or III in Braunwald classification of unstable angina. Coronary angiograms were performed for all patients using standard techniques within 1 week of admission. Twenty patients had single vessel disease and 24 patients had multivessel disease. Only the 24 patients displaying multivessel disease were eligible for our study.

Dual SPECT imaging

Within 7 days after coronary angiography (mean 3.4 days), all 24 patients underwent BMIPP/Tl dual SPECT. 111MBq of both tracers was injected intravenously. Dual SPECT imaging was started approximately 30 min after injection. The energy window setting was around the 70 KeV (25% window) X-ray emission of the mercury daughter of Tl and around the 159 KeV (20% window) X-ray emission of the mercury daughter of BMIPP. Images were acquired using a gamma camera with a large view field and equipped with an energy general purpose collimator that was rotated around the patient over a range of 180 degrees at intervals of 6 degrees for 30 sec/image. Oblique angle tomograms (long-axis, short-axis, and horizontal long-axis reconstructions) were obtained from dual SPECT images. No cross-talk correction was applied. The pattern of uptake activity was evaluated by both visual



Activity: Normal;>80% of normal area Mildly reduced;50% to 80% Severely reduced;<50%

Fig. 1 Diagram of left ventricular myocardial segments

and circumferential analysis. The uptake was considered normal if activity was more than 80% of the normal area, mildly reduced if 50% to 79%, and severely reduced if less than 50%. The regional activities in the four quadrants of the short-axis slices were measured from basal, mid, and apical sets. Each slice was divided into the myocardial segments and matched according to the coronary artery distribution as follows; septal and anterior segments corresponded to the left anterior descending artery (LAD), inferior segments to the right coronary artery (RCA), and lateral and posterior segments to the left circumflex coronary artery (LCX). No isolated apical perfusion was assigned to any of the three particular flow regions (Fig. 1). We attempted to identify the causative lesion of the multivessel disease based on the patterns on BMIPP/Tl dual SPECT images.

Echocardiography

Wide-angle, two-dimensional echocardiograms were obtained using multiple standard echocardiographic views including the parasternal long-and short-axis or two-chamber and the subcostal four-chamber views. The echocardiographic studies were performed consecutively in all 24 patients prior to the dual SPECT studies. Echocardiographic assessment of regional wall motion was made dividing the different walls into upper, middle and distal segments. Both systolic wall thickening and inward wall motion were evaluated visually.

Management plan

We planned the following management of each patient based on the results of the dual SPECT study (**Fig. 2**). The subsequent interventions were performed with the strategy to dilate only the lesion which was detected by BMIPP SPECT imaging.

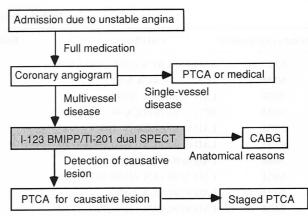


Fig. 2 Flow chart of management plan

RESULTS

Clinical and nucleological characteristics of study group

Table 1 shows the findings on coronary angiogram, dual SPECT and echocardiogram in individual patients. All patients had decreased uptake area of BMIPP activity. In contrast, only three patients showed abnormal defects on Tl imaging. Echocardiogram could reveal the ischemic lesion in only a few patients.

Correlation of BMIPP with thallium-201 SPECT (Table 2)

In BMIPP SPECT there were 4 segments (1.4%) with severe decreases in activity, 70 (24.3%) with mild decreases in activity, and 214 segments (74.3%) with normal uptake. In contrast, Tl SPECT showed normal uptake in 68 of 74 segments with abnormal BMIPP activity. In addition, the sizes of reduced uptake area in BMIPP SPECT were larger than in Tl SPECT. Areas with decreases in BMIPP uptake were demonstrated in all 24 patients. All segments with abnormal BMIPP uptake were well correlated to the locations consisting of severe stenosis in the coronary angiograms. Accordingly, the lesion causing the unstable angina in patients with multivessel disease could be detected by BMIPP SPECT (Fig. 3). The lesions were detected on the LAD in 12 patients, on the LCX in 5 patients, and on the RCA in 7 patients.

Approach to management

Based on the identification of the causative lesion by BMIPP SPECT, we managed 24 patients with multivessel disease (**Fig. 4**). Thirteen patients un-

Table 1	Dationt	charac	teristics
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Patients (age/gender)	CAG findings	BMIPP defect area	Tl defect area	Echo hypokinetic area
63/F	LAD 7) 75, RCA 1) 100, Ao-LCX 90	Posterior	_	-
60/M	LCX 11) 99, RCA 3) 90	Posterior	_	_
50/M	LAD 7) 90, LCX 14) 90	Anterior	_	_
58/M	RCA 2) 90, Ao-LCX 90	Posterior	_	-
75/M	LAD 6) 100, LCX 11) 100	Anterior	_	Anterior
63/M	LAD 6) 90, LCX 13) 90, RCA 4) 90	Anterior	-	-
58/M	LAD 6) 90, LCX 14) 90	Anterior	-	-
64/M	LAD 7) 99, LCX 14) 90, RCA 1) 100	Anterior	Anterior	Anterior
56/M	LAD 6) 90, RCA 2) 99	Inferior	-	-
74/M	LAD 8) 90, LCX 11) 99, RCA 1) 100	Inferior	_	-
76/F	LAD 6) 99, LCX 12) 99, RCA 2) 90	Anterior	Anterior	Apex
58/M	LAD 7) 90, RCA 1) 90	Inferior	Inferior	-
45/F	LCX 13) 90, RCA 3) 99	Inferior	-	-
69/M	LMT 90, LAD 6) 99, LCX 14) 90	Anterior	_	Generalized hypokinesis
61/M	D1 9) 99, LCX 13) 99	Posterior	_	-
71/M	LAD 7) 90, LCX 11) 90, RCA 2) 75	Anterior	-	_
56/M	LAD 7) 75, LCX 12) 75	Posterior	_	=
48/M	LAD 8) 99, RCA 3) 90	Inferior	-	Apex
74/F	LMT 50, LAD 7) 75, RCA 2) 90	Anterior	-	-
62/M	LAD 6) 100, LCX 14) 90	Anterior	-	-
58/M	LAD 6) 90, LCX 12) 100	Anterior	_	-
74/M	LAD 6) 90, RCA 1) 90	Inferior	_	-
57/F	LAD 7) 90, D1 90, LCX 12) 99	Anterior	=	-
68/M	LAD 6) 90, RCA 4) 99	Inferior	_	_

The column CAG findings shows the artery and segment identity number harboring the causative lesion, and the percentage stenosis.

Ao-LCX=aortic left circumflex coronary artery; LMT=left main coronary trunk; D1=diagonal 1; CAG=coronary angiography; M=male; F=female.

Table 2 Comparison of segmental analysis of thallium-201 and BMIPP SPECT images

	TI-201 SPECT		
BMIPP SPECT	Normal	Mildly reduced	Severely reduced
Normal	214 (74.3%)	0	0
Mildly reduced	68 (23.6%)	2 (0.7%)	0
Severely reduced	0	4 (1.4%)	0

BMIPP SPECT showed 4 segments with severe decreases, 70 with mild decreases, and 214 segments with normal uptake of BMIPP activity. In contrast, Tl-201 SPECT showed normal uptake in 68 of 74 segments with abnormal BMIPP activity.

derwent balloon angioplasty of the lesion detected by BMIPP. Palmaz-Schatz stents were implanted in five patients at the lesion. Ten of the 18 patients who received coronary intervention for the lesion underwent some further dilatation at a later date. Six patients underwent urgent coronary artery bypass grafting of anatomically inaccessible lesions. All

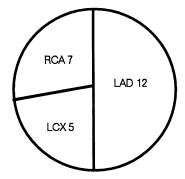


Fig. 3 Prediction of lesion causing unstable angina in patients with multivessel disease with BMIPP SPECT

The lesions were detected on the LAD in 12, on the LCX in 5, and on the RCA in 7 patients.

were discharged in satisfactory condition.

Case presentation

A representative example is shown in **Fig. 5**. This patient was a 63-year-old female who received a coronary artery bypass grafting to the LCX 7 years ago. She was admitted because of recurrent epi-

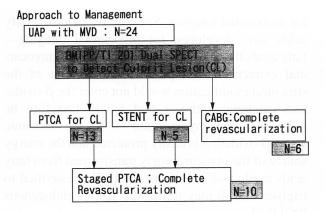


Fig. 4 Management of 24 patients with multivessel disease

Thirteen patients received balloon angioplasty to the lesion detected by BMIPP. Five patients underwent stent implantation on the lesion. Ten of 18 patients who received coronary intervention required further angioplasty at a later date. Six patients underwent coronary bypass surgery. All patients were discharged in satisfactory condition.

UAP=unstable angina pectoris; MVD=multivessel disease.

sodes of angina, and demonstrated reversible electrocardiogram changes of ischemia at rest for 15 min. She had severe symptoms despite medical therapy. Coronary arteriography was performed 2 days after admission. She had multivessel disease; mid portion of LAD was 75% occluded, the aorta to LCX vein graft was 90% occluded, and the RCA was totally occluded. She underwent BMIPP/Tl dual SPECT on the same day. A BMIPP defect appeared on the posterolateral segment, while the Tl image showed normal perfusion. Based on the dual SPECT images, we suggested the causative lesion was the stenosis located in the vein graft to the LCX. Therefore, we implanted a Palmaz-Schatz stent in the vein graft. She was discharged in a satisfactory condition 8 days after implantation of the stent.

DISCUSSION

Management of patients with unstable angina

Unstable angina is, by definition, a state of instability leading either to improvement or to myocardial infarction or death^{10,11}). Treatment is directed

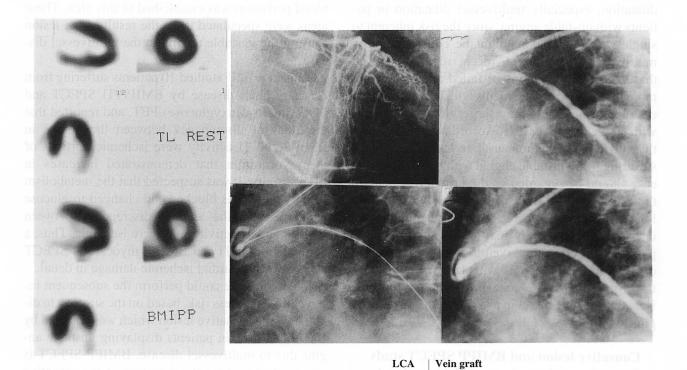


Fig. 5 Representative case

Left: TI-201 SPECT scan showing normal myocardial perfusion. BMIPP SPECT showed mildly decreased BMIPP activity on the posterolateral segment. A discrepancy between TI-201 and BMIPP SPECT was observed. Right: The causative lesion was the stenosis located in the vein graft to LCX. This patient received a Palmaz-Schatz stent implantation on the vein graft to LCX. The residual stenosis of vein graft was 10% compared to 90% occlusion before stenting.

Post stent

Stenting

first towards initial relief of acute ischemic symptoms and second towards prevention of progression to myocardial infarction or death. The exact causes of unstable angina are not established, and several conditions either alone or in combination may be responsible. In fact, unstable angina is nearly always associated with a high grade, fixed coronary stenosis^{12,13)} and it is very likely that dynamic conditions at this fixed stenosis are involved. Despite growing experience with coronary angioplasty for the treatment of unstable angina, coronary angioplasty in patients with initially stabilized unstable angina has a somewhat lower success rate (85–88%) and a higher major complication rate (emergency surgery and acute myocardial infarction) than angioplasty in patients with stable angina^{14,15)}.

The majority of patients with unstable angina have multivessel disease^{16,17)}. Successful dilatations in single-vessel angioplasty procedures have been performed with acceptable complication rates in patients with stable angina^{18,19}). However, there is less acceptance of and less experience with multivessel dilatation, especially multivessel dilatation in patients with unstable angina, since the risk inherent to single-vessel dilatation might be compounded by multivessel dilatation. A recent report²⁰⁾ showed that major complications or failed angioplasty are more likely to occur in patients with multivessel disease requiring emergency surgery than in patients with single-vessel disease. Accordingly, we believe that angioplasty of the causative lesion in patients suffering from unstable angina with multivessel disease should be regarded as the primary strategy in the acute stage. In most patients, this will result in long-term success, whereas some further dilatations or even bypass surgery may be required. In these patients, subsequent interventions can be performed on a more elective basis with less risk. We have therefore adopted the concept of dilating only the ischemia-related vessel in patients with unstable angina and multivessel disease21).

Causative lesion and BMIPP SPECT study

Currently, we do not have a reliable tool to detect the causative lesion in multivessel coronary artery disease. Fatty acids provide the major energy source for normal myocardium. The efficient extraction of various radiolabeled fatty acids from plasma has led to the development and evaluation of such agents for myocardial imaging. Structurally modified fatty acids were developed for myocardial imaging—fatty acids that would show rapid, efficient myocardial extraction from plasma, but because of the structural modification would not enter the β -oxidation catabolic pathway and would therefore be trapped in the myocardium¹⁻³⁾. In the ischemic stage, β -oxidation is easily protected and the energy source of the myocardium is transformed from fatty acids to glucose²²⁾. Because BMIPP is esterified to triglycerides, it may reflect the size of endogenous lipid pool.

We are able to demonstrate the ischemic myocardium as the decreased area of fatty acid metabolism by activity in BMIPP. We studied the patients of unstable angina with multivessel disease to evaluate the characteristic findings of BMIPP myocardial images. In our study, discrepancies between BMIPP- and Tl-imaged defects were frequently observed in patients displaying unstable angina with multivessel disease. Thus, myocardial uptake of BMIPP was depressed in the area characterized by severe ischemia, whereas satisfactory myocardial blood perfusion was established in this area. These areas were speculated to be the result of the lesion causing the unstable angina in the multivessel disease.

Tamaki *et al.*²³⁾ studied 10 patients suffering from coronary heart disease by BMIPP/Tl SPECT and FDG (fluoro-deoxyglucose)-PET, and reported that the areas of discrepancy between the uptake in BMIPP and Tl activity were ischemic portions of the myocardium that demonstrated increases in FDG activity. It was suspected that the metabolism of fatty acids was blocked and changed to glucose metabolism in the area of discrepancy between BMIPP and Tl activity by severe ischemia. Thus, a combination of Tl and BMIPP myocardial SPECT can assess myocardial ischemic damage in detail.

In addition, we could perform the subsequent intervention with less risk, based on the strategy to dilate only the causative lesion which was detected by BMIPP SPECT in patients displaying unstable angina due to multivessel disease. BMIPP SPECT is an excellent tool for the detection of the causative lesion in unstable angina.

Cross talk correction

The difficulty in performing dual isotope studies is an unavoidable overlapping of the spectra of both

isotopes, especially with the spill-over of scattered thallium-201 photons into the iodine-123 energy window. This phenomenon is especially detrimental in a scatter-rich environment such as the human chest. Different corrections for thallium-201 spill-over or special energy-weighted are proposed²⁴⁾ but are yet not clinically validated. This study is in essence a non-quantitative comparison of thallium-201 versus iodine-123 images. Thallium interference on BMIPP images was not significant with our protocol for the comparison of visual data between sets of Tl and BMIPP images.

CONCLUSION

Coronary angioplasty in patients with unstable angina is restricted to a limited number of patients, even only the causative lesion is dilated in patients with multivessel disease. The causative lesion causing unstable angina in patients with multivessel disease can be detected by BMIPP SPECT before angioplasty with less risk. Based on the available evidence in our study, we propose the above management of patients with unstable angina.

要約

不安定狭心症多枝病変例における治療戦略の考察: Iodine-123-Betamethyl-p-Iodophenyl-Pentadecanoic Acid シンチグラムの有用性の検討

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Iodine-123-betamethyl-p-iodophenyl-pentadecanoic acid (BMIPP) は、心筋の虚血による脂肪酸代謝障害を鋭敏に画像化できるという特徴を持つ心筋血流イメージング製剤である.

我々は、多枝疾患不安定狭心症 24 例を対象に、BMIPP/Tl dual SPECT を平均 3.4 病日に施行し、両者の画像を比較した、短軸像の心基部、中部、心尖部に対して、それぞれを 4 分割し、各区域ごとに正常部との集積の程度から 3 段階に評価した(正常部の 80%以上の活性は正常集積、50-79%は軽度集積低下、50%未満は高度集積低下). また、入院後 1 週間以内に冠動脈造影を施行した。Dual SPECT の欠損領域から、障害となる冠動脈病変を推定し、インターベンションの手順を決定するという管理計画を作った。

SPECT の解析では、BMIPP において、214 分画では正常であったが、70 分画 (24.3%) に軽度 の活性低下、4 分画 (1.4%) には更に重篤な低下を呈していた。一方、Tl では、BMIPP で異常 を呈した74 分画のうち、68 分画は正常な活性を示した。更に、BMIPP の活性低下部位は、 冠動脈造影上の障害病変に該当すると考えられた。この結果に基づき、全症例に血行再建術 (PTCA、CABG) が安全に施行された。

BMIPP の活性低下は,不安定狭心症多枝疾患例に多く認められた. BMIPP SPECT は障害病変の同定のためには有用な武器であり,更にその結果に基づき,推定障害病変から着手するという戦略で行われるインターベンションは安全に施行可能で,良好な成績を得ることができた.

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