Iodofiltic Acid I 123 (BMIPP) Fatty Acid Imaging Improves Initial Diagnosis in Emergency Department Patients With Suspected Acute Coronary Syndromes
A Multicenter Trial

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Objectives
The aim of this study was to assess the performance of β-methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT) to detect acute coronary syndromes (ACS) in emergency department patients with chest pain.

Background
Emergency department diagnosis of chest pain is problematic, often requiring prolonged observation and stress testing. BMIPP SPECT detects abnormalities in fatty acid metabolism resulting from myocardial ischemia, even many hours after symptom cessation.

Methods
Emergency department patients with suspected ACS were enrolled at 50 centers. Patients received 5 mCi BMIPP within 30 h of symptom cessation. BMIPP SPECT images were interpreted semiquantitatively by 3 blinded readers. Initial clinical diagnosis was based on symptoms, initial electrocardiograms, and troponin, whereas the final diagnosis was based on all available data (including angiography and stress SPECT) but not BMIPP SPECT. Final diagnoses were adjudicated by a blinded committee as ACS, intermediate likelihood of ACS, or negative for ACS.

Results
A total of 507 patients were studied and efficacy was evaluated in 448 patients with sufficient data. The sensitivity of BMIPP by 3 blinded readers for a final diagnosis of ACS and intermediate likelihood of ACS was 71% (95% confidence interval [CI]: 64% to 79%), 74% (95% CI: 68% to 81%), and 69% (95% CI: 62% to 77%); the corresponding specificity of BMIPP was 67% (95% CI: 61% to 73%), 54% (95% CI: 48% to 60%), and 70% (95% CI: 64% to 76%). Compared with the initial diagnosis alone, BMIPP initial diagnosis increased sensitivity from 43% to 81% (p < 0.001), negative predictive value from 62% to 83% (p < 0.001), and positive predictive value from 41% to 58% (p < 0.001), whereas specificity was unchanged (61% to 62%, p = NS).

Conclusions
The addition of BMIPP data to the initially available clinical information adds incremental value toward the early diagnosis of an ACS, potentially allowing determination of the presence or absence of ACS to be made earlier in the evaluation process. (Safety and Efficacy Iodofiltic Acid I 123 in the Treatment of Acute Coronary Syndrome [Zeus-ACS]; NCT00514501) (J Am Coll Cardiol 2010;56:290–9) © 2010 by the American College of Cardiology Foundation
Patients presenting to emergency departments (EDs) with chest pain and other symptoms consistent with an acute coronary syndrome (ACS) represent a common problem (1,2). In the absence of high-risk findings, the overall risk is low but not negligible. Importantly, this low-risk group of patients accounts for nearly two-thirds of ED chest pain patients (3). Accurately identifying the relatively few high-risk patients among this large number of low-risk patients is often challenging.

In an effort to accelerate this diagnostic process, a number of newer tools have been investigated. In this regard, rest myocardial perfusion imaging (MPI) using technetium radiopharmaceuticals has been shown to be a valuable technique (4). Numerous observational studies and a large randomized clinical trial demonstrated high accuracy for the detection of myocardial infarction (MI) and ACS and favorable effects on clinical decision making (5–9). MPI adds incremental diagnostic and prognostic value when used in conjunction with clinical data (5–9). MPI randomized clinical trial demonstrated high accuracy for the technique (4). Numerous observational studies and a large radiopharmaceutical has been shown to be a valuable myocardial perfusion imaging (MPI) using technetium-99m-labeled perfusion imaging agents such as thallium-201 and rubidium-82 or technetium-99m-labeled perfusion imaging agents such as tetrofosmin and tetrafosmin, respectively.

The purpose of this study was to evaluate the efficacy and safety of BMIPP in patients who presented to an ED with symptoms suggestive of ACS. The high-risk patients were stratified into 1 of 3 risk strata, high, moderate, or low likelihood of ACS, to ensure that a sufficient number of patients who would ultimately be “truth standard positive” would be enrolled. Criteria for stratification were as follows: patients in the high likelihood stratum had new or presumably new ST-segment depression ≥1 mm on ≥1 ECG leads consistent with ischemia or initial cardiac troponin T or troponin I markers that were elevated above the institution’s diagnostic level for MI. Patients in the moderate likelihood stratum had no features of the high likelihood group, but a history of coronary artery disease (CAD), defined as a previous angiography with ≥50% stenosis or previous revascularization, and symptoms consistent with ACS (with an accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or with minimal effort). Patients in the low likelihood stratum had no features of the high or intermediate likelihood group, had a nonischemic ECG, and either an episode of typical ACS chest pain and related symptoms >20 min without a history of CAD or an episode of atypical chest pain symptoms >20 min with a history of CAD.

Clinical and imaging data acquisition. For each participant, the following data were acquired: assessment of symptoms, coronary angiographic data (if clinically indicated), rest/stress SPECT data, cardiac biomarkers, adverse events, and BMIPP SPECT images. Angiographic and SPECT images were forwarded to a core laboratory for evaluation by independent readers blinded to patient information other than sex, height, and weight. BMIPP images were acquired during the course of the patient’s clinical care, but per protocol, the BMIPP data were not to be used to influence the clinical course.

BMIPP imaging and analysis. Each study patient was to receive a single injection of 5.0 mCi of BMIPP, containing 18.5-iodo-6-iodophenyl-11-cis-retinal (BMIPP) is a methyl branched-chain fatty acid that is not easily metabolized and thus is retained in myocardial cells (15). Clinical studies have demonstrated persistent reductions in BMIPP uptake long after resolution of ischemic symptoms (16–18). Therefore, BMIPP imaging may extend the window of time for identification of myocardial ischemia after symptom resolution, even after restoration of myocardial blood flow (19).

The purpose of this study was to evaluate the efficacy and safety of BMIPP in patients who presented to an ED with symptoms suggestive of ACS.

Methods

Study population. Patients eligible for this study were drawn from those with symptoms consistent with or possibly consistent with ACS who were admitted to an ED at 1 of 50 clinical sites in the U.S. and Canada. Patients were 40 years of age and older; not of child-bearing potential; without a history of MI; and without ST-segment elevation, left bundle branch block, or Q-wave abnormalities on an electrocardiogram (ECG) consistent with previous MI. Patients were excluded if they had a left ventricular ejection fraction ≤40%, serum creatinine >2.0 mg/dl; an allergy to X-ray contrast media or iodine/iodides, received any other radiopharmaceutical (other than rubidium-82 or thallium-201), or had undergone cardiac stress testing of any kind within 2 days before enrollment in the study. It was required that patients be imaged with BMIPP within 30 h of the cessation of symptoms.

At enrollment, patients were stratified into 1 of 3 risk strata, high, moderate, or low likelihood of ACS, to ensure that a sufficient number of patients who would ultimately be “truth standard positive” would be enrolled. Criteria for stratification were as follows: patients in the high likelihood stratum had new or presumably new ST-segment depression ≥1 mm on ≥1 ECG leads consistent with ischemia or initial cardiac troponin T or troponin I markers that were elevated above the institution’s diagnostic level for MI. Patients in the moderate likelihood stratum had no features of the high likelihood group, but a history of coronary artery disease (CAD), defined as a previous angiography with ≥50% stenosis or previous revascularization, and symptoms consistent with ACS (with an accelerating pattern or prolonged [>20 min] or recurrent episodes at rest or with minimal effort). Patients in the low likelihood stratum had no features of the high or intermediate likelihood group, had a nonischemic ECG, and either an episode of typical ACS chest pain and related symptoms >20 min without a history of CAD or an episode of atypical chest pain symptoms >20 min with a history of CAD.
up to 0.5 mg of iodofilitic acid, within 30 h of symptom cessation. Imaging was begun within 10 min of BMIPP injection. For each patient, a total of 60 to 94 tomographic SPECT projections were acquired on a dual-head gamma camera in an 180° arc from right anterior oblique to left posterior oblique, using a step-and-shoot technique, over approximately 22 min. All raw, unprocessed SPECT data were collected from the sites by a central core laboratory. The core laboratory reconstructed all the raw SPECT data using the same filtered back-projection technique and filter settings on a single workstation to achieve uniform reconstruction. All analyses were then performed on the uniformly processed data. Raw data were reconstructed into transaxial slices by using filtered back-projection techniques at the core imaging laboratory. A Butterworth filter (0.5 cutoff, 0.5 order) was applied to all patient data using a Siemens Syngo workstation (Siemens Medical Solutions, Malvern, Pennsylvania) and reoriented into short-axis slices. Three-dimensional left ventricular BMIPP count distributions were analyzed within the QPS (Cedars Sinai Med-

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**Figure 1** Schematic of Patient Disposition and Analysis Groups

Subcategories not mutually exclusive. ACS = acute coronary syndrome; Angio = angiography; CABG = coronary artery bypass graft; ECG = electrocardiogram; MPI = myocardial perfusion imaging; PCI = percutaneous coronary intervention; SDS = summed difference score; TnI = troponin I; TnT = troponin T; ULN = upper limit of normal.
ical Center, Los Angeles, California) semiautomatic nuclear cardiology software package. Each patient’s 3-dimensional count distribution was quantitatively compared with the mean normal regional distribution from a sex-matched normal database (40 males, 40 females) prospectively developed in another study (BMIPP SPECT images were oped in another study (BMIPP SPECT images were developed). The criterion for abnormality in each pixel was >2.5 SDs below the mean normal distribution. Three independent readers assessed and recorded segmental scores based on a 5-point scale representing the severity and extent of abnormality using a 17-segment model (following American Society of Nuclear Cardiology/American College of Cardiology standards) (20), based on visual review of the patients’ image data, the raw data, and the quantitative analysis. Readers were presented with the software-generated segmental scores produced by the software package and were instructed to use those scores as a guide for their visual analysis. However, the readers had to enter their own segmental scoring in the electronic case report form.

Based on the earlier phase 2 studies, a cutoff value of 3 for the summed segmental score of BMIPP was chosen to guide the blinded readers to optimize diagnostic performance. After recording segmental scores, readers were asked to categorize the image as normal or abnormal.

**Analysis of coronary angiographic data.** Angiographic images were analyzed at a central imaging laboratory, blinded to the BMIPP imaging data. The potential presence of a culprit lesion was assessed through ulceration and thrombus severity scoring. The percentage of stenosis and potential culprit lesion for each of 3 coronary territories were based on segmental results within each territory. In addition, collateral blood flow was also evaluated for each of the 3 territories (21–23).

**Algorithms for the initial clinical diagnosis.** To quantitate the potential value of BMIPP imaging when added to the initial clinical information, an algorithm for determining the initial clinical diagnosis was prospectively defined and was used by an adjudicator (blinded to the BMIPP data) to review available initial clinical data and arrive at one of the following initial diagnoses for each patient: 1) positive for ACS, defined as a positive ECG or troponin at the time of ED admission; 2) equivocal for ACS, defined as at least 1 of the following criteria: borderline troponin, a borderline ECG, or a negative troponin/negative ECG/positive typical chest pain symptoms; or 3) negative for ACS, defined as a negative ECG and troponin and borderline symptoms. For the calculations of both sensitivity and specificity for the initial clinical diagnosis category, equivocal patients were counted as incorrect.

**Adjudication of the truth standard for the final diagnosis.** An algorithm for determining the final diagnosis (truth standard) was defined prospectively to guide a 2-member Final Diagnosis Adjudication Committee, which reviewed patient data independently to determine a final diagnosis (Fig. 1). ACS as a final diagnosis was defined as a positive cardiac troponin on serial testing, ≥2 mm ST-segment depression on initial or serial ECGs, and/or a culprit lesion visible on angiography, as well as patients who had angiography showing ≥90% stenosis, a stress MPI result positive for inducible ischemia, and/or coronary revascularization, MI, or death during 30 days of follow-up. Disagreements were resolved by consensus.

Recognizing that ACS is a syndrome that may be diagnosed with less clear evidence, a final diagnosis category of intermediate likelihood of ACS was defined as a subset of patients with more limited evidence of ACS, such as only borderline cardiac troponin or angiography showing 70% to 89% stenosis only (no culprit lesion) or a subsequent percutaneous coronary intervention with stress MPI negative or not done.

**Safety analysis.** The safety of BMIPP was evaluated by comparing baseline and post-injection ECGs, vital signs,

### Table 1 Demographic and Baseline Characteristics of Patients With Signs and Symptoms of ACS Dosed With Iodofiltic Acid I 123

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dosed Population (N = 507)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>275 (54.2)</td>
</tr>
<tr>
<td>Female</td>
<td>232 (45.8)</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.2 (12.2)</td>
</tr>
<tr>
<td>Range (minimum, maximum)</td>
<td>30, 97</td>
</tr>
<tr>
<td>&lt;40</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>40–49</td>
<td>122 (24.1)</td>
</tr>
<tr>
<td>50–59</td>
<td>164 (32.3)</td>
</tr>
<tr>
<td>60–69</td>
<td>123 (24.3)</td>
</tr>
<tr>
<td>≥70</td>
<td>97 (19.1)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>393 (77.5)</td>
</tr>
<tr>
<td>Black</td>
<td>83 (16.4)</td>
</tr>
<tr>
<td>Other (Asia Pacific, American Indian)</td>
<td>30 (5.9)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>66 (13.0)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>441 (87.0)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>87.4 (21.0)</td>
</tr>
<tr>
<td>Range (minimum, maximum)</td>
<td>47, 166</td>
</tr>
<tr>
<td><strong>History of</strong></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>102 (20.1)</td>
</tr>
<tr>
<td>CAGB</td>
<td>36 (7.1)</td>
</tr>
<tr>
<td>HTN</td>
<td>353 (69.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>139 (27.4)</td>
</tr>
<tr>
<td><strong>Cardiac medication</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>440 (86.8)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>322 (63.5)</td>
</tr>
<tr>
<td>ACEIs</td>
<td>185 (36.5)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>312 (61.5)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>471 (92.9)</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise indicated.

ACEI = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; CAGB = coronary artery bypass grafting; CAD = coronary artery disease; HTN = hypertension.
and clinical laboratory measurements. Patients were monitored for adverse events from the time informed consent was signed through 20 to 30 h after administration of BMIPP and were followed for up to 30 days to collect data for any serious adverse events, subsequent stress perfusion studies, or intervening cardiac events.

Data and statistical analysis. Sensitivity and specificity for the analysis of BMIPP SPECT images alone, for the initial clinical diagnosis alone, and the initial clinical diagnosis plus the BMIPP SPECT imaging result each were calculated in comparison with the truth standard for ACS. The added clinical utility of BMIPP SPECT imaging for patients with symptoms suggestive of ACS was determined by comparing the improvement in diagnostic accuracy obtained by including the interpretation of BMIPP SPECT imaging results, along with clinical data available at presentation, when making the interpretation of BMIPP SPECT imaging results, along with clinical data available at presentation, when making the diagnosis and then comparing these results with the diagnostic accuracy attained using initial clinical data alone, using McNemar’s test of paired proportions (24). The statistical significance of the comparisons for positive and negative predictive values between the 2 diagnostic strategies was assessed using the bootstrap resampling method via 5,000 simulations (25). Net reclassification improvement was calculated based on the method proposed by Percina et al. (26). For all estimates, a 95% confidence interval (CI) (exact binomial distribution) was calculated.

Table 2  Sensitivity and Specificity for BMIPP SPECT Images for the Efficacy Population (n = 448)

<table>
<thead>
<tr>
<th>Variable (by ACS Category)</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
<th>Majority Read</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS (n = 129)</td>
<td>75.9 (88/116)</td>
<td>78.0 (99/127)</td>
<td>74.8 (86/115)</td>
<td>76.3 (90/118)</td>
</tr>
<tr>
<td>ACS and intermediate likelihood ACS (n = 176)</td>
<td>71.3 (114/160)</td>
<td>74.4 (128/172)</td>
<td>69.4 (111/160)</td>
<td>73.0 (110/163)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative ACS (n = 273)</td>
<td>66.6 (165/247)</td>
<td>54.0 (147/272)</td>
<td>69.6 (172/247)</td>
<td>63.2 (160/253)</td>
</tr>
</tbody>
</table>

Values are % (n/N), 95% confidence interval. The denominator is different for each reader and for the majority read because images assessed by each reader as nondiagnostic or with constraint/contour error during image processing were excluded for each reader. The majority read was determined based on the consensus of 2 of the 3 readers. The majority read was undetermined for a study image when ≥2 readers rated it as nondiagnostic or with constraint error or 1 reader rated the image as nondiagnostic and 2 other readers disagreed.

Results

Study population. Table 1 summarizes patient demographic and baseline characteristics for all dosed patients (n = 507); 3 enrolled patients were not dosed, 2 due to unavailability of study radiopharmaceutical.

Figure 1 shows the patient disposition for both safety and efficacy populations. To be included in the efficacy analysis, each patient must have had sufficient data available for the Final Diagnosis Adjudication Committee to make a definite final diagnosis. Of the 507 dosed patients, 59 were excluded from analysis. Five patients had a protocol exclusion criteria violation, 4 patients did not complete BMIPP SPECT imaging, and 54 patients did not have angiography or protocol-specified stress MPI during the 30-day follow-up period. These categories were not mutually exclusive. The efficacy population consisted of 448 patients who underwent BMIPP SPECT imaging and received an adjudicated final diagnosis from the Final Diagnosis Adjudication Committee.

Efficacy of BMIPP SPECT imaging. BMIPP SPECT imaging was performed at a mean of 11.9 ± 9.8 h after cessation of symptoms. Time of chest pain cessation was available for 433 patients. Imaging was performed >12 h after chest pain cessation for 46%, between 0 to <12 h for 52%, and while chest pain was ongoing in 2% of patients. Of 448 BMIPP images in the efficacy population, image quality was rated as excellent, good, or diagnostic in 96% to 99% of cases across the 3 blinded readers.
Performance characteristics for each individual blinded reader for overall diagnosis and for each subcategory of ACS diagnosis are shown in Table 2. For the diagnosis of ACS, the sensitivities for each reader as well as the majority read were 75% to 80%.

Table 3 summarizes sensitivity and specificity results for the initial clinical diagnosis alone, for BMIPP SPECT imaging alone (based on the majority read), and for the initial clinical diagnosis with the added information from BMIPP SPECT imaging. For the diagnosis of ACS, BMIPP SPECT imaging alone provided higher sensitivity than the initial clinical diagnosis alone (73% vs. 43%, \( p < 0.001 \)). Combining information from both the initial clinical diagnosis and BMIPP SPECT images resulted in significantly higher sensitivity (81%, McNemar’s test, \( p < 0.001 \)) compared with the sensitivity (43%) for the initial clinical diagnosis alone. This increase in sensitivity was associated with no change in specificity because the specificity of BMIPP SPECT imaging alone was similar to that of the initial clinical diagnosis alone (63% vs. 61%, respectively). The specificity of the combination of initial clinical information and BMIPP SPECT imaging was also similar (62%). The negative predictive value increased significantly, from 62% for the initial clinical diagnosis alone to 83% for the combined initial clinical information and BMIPP SPECT imaging (\( p < 0.001 \)). The positive predictive value increased as well, from 41% for the initial clinical diagnosis alone to 58% when BMIPP SPECT imaging results were added (\( p < 0.001 \)).

Among all patients, net reclassification improvement was 8.5% (\( p = 0.13 \) vs. 0%), and among those patients whose initial clinical diagnosis was equivocal or negative, the net reclassification improvement was 32% (\( p < 0.001 \) vs. 0%).

**Correlation of BMIPP imaging with coronary angiography and culprit lesion anatomy.** A subgroup analysis was performed to assess the performance of BMIPP SPECT imaging among those patients who underwent angiography (n = 198), stratified by the presence/absence of a potential culprit lesion and the presence/absence of collateral blood flow (Table 4). BMIPP SPECT imaging had sensitivities for ACS with a culprit lesion present of 84% to 86% across the 3 readers. When these data were stratified by the presence/absence of collateral blood flow, the sensitivities were 90% to 96% when collateral blood flow was absent and 75% to 82% when collateral blood flow was present (Figs. 2 and 3). The sensitivities of BMIPP were lower for ACS without a culprit lesion present: 57% to 74%, across 3 readers, for any stenosis >70% but without angiographic features of a culprit lesion.

**Influence of duration from cessation of symptoms on BMIPP performance.** Among patients who were imaged with BMIPP <12 h after symptom resolution, sensitivity for detection of the truth standard final diagnosis was 77.1% (95% CI: 66.6% to 87.7%) based on the

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**Table 4** Evaluation of BMIPP SPECT Imaging Compared With Angiography Results: Correlation With Culprit Lesion Anatomy

<table>
<thead>
<tr>
<th>Culprit Lesion Present on Angiography</th>
<th>With Collateral Blood Flow</th>
<th>Without Collateral Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85.7 (54/64), 74.8–95.6</td>
<td>81.5 (22/27), 65.0–98.0</td>
</tr>
<tr>
<td>2</td>
<td>84.0 (58/69), 76.5–94.5</td>
<td>81.5 (22/27), 65.0–98.0</td>
</tr>
<tr>
<td>3</td>
<td>84.0 (58/69), 76.5–94.5</td>
<td>81.5 (22/27), 65.0–98.0</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
majority read, whereas among patients who were imaged 12 to 30 h after symptom resolution, sensitivity was 68.6% (95% CI: 58.2% to 79.0%) based on the majority read. The receiver-operator characteristic curve assessing the ability of BMIPP imaging to discriminate the presence and absence of the ACS truth standard, with patients classified as those imaged ≤12 h versus those imaged ≥12 h after symptom resolution, is shown in Figure 4. The area under the receiver-operator characteristic curve was similar for both groups (for ≤12 h, the area under the curve = 0.710; for ≥12 h, the area under the curve = 0.714).

Safety of BMIPP. Of 507 patients who received BMIPP, 109 patients (21.5%) reported a total of 209 adverse events. Of these, 164 (78.5%) events were judged by the physician to be unrelated to BMIPP use. Most adverse events were mild in severity. Serious adverse events were reported by 27 (5.3%) patients, and 4 deaths (lung cancer, MI, cardiac arrest, progressive CAD) occurred during the study or within the 30-day follow-up period after dosing with BMIPP (none were attributed by the investigators to BMIPP).

The most common adverse event was headache (3.9% of patients); none were rated severe, and most (17 of 20) were attributed to BMIPP administration by the investigators. Clinical laboratory values and vital signs showed only clinically insignificant changes from baseline after BMIPP dosing.

**Discussion**

The current trial was carried out in contemporary ED practice, assessing patients presenting with chest pain symptoms suggestive of an ACS. The results suggest that assessing fatty acid metabolism with BMIPP SPECT imaging has overall sensitivity comparable to that of other imaging modalities in use for this situation and also adds incremental diagnostic value to the initial clinical information available to clinicians. Moreover, taking advantage of the concept of ischemic memory—the prolonged suppression of fatty acid metabolism after an episode of ischemia—BMIPP imaging seems to maintain sensitivity even when performed hours after the ischemic symptoms have resolved.

The direct imaging of the metabolic consequence of tissue ischemia and the ability to capture such data many hours after symptom cessation are unique properties.

The feasibility of using metabolic imaging to detect ischemic myocardium was first demonstrated by Schelbert et al. (27) in a canine model. In the ischemic segments, they observed a decrease in fatty acid utilization (assessed by C-11 palmitate) and an increase in glycolytic flux (assessed by fluorodeoxyglucose positron emission tomography). In subsequent occlusion–reperfusion studies in canines, Schwaiger et al. (28) showed prolonged metabolic alteration after 30 min of coronary occlusion that persisted for several weeks thereafter. These studies served as the experimental basis of subsequent clinical studies in human subjects for using metabolic imaging (fluorodeoxyglucose and BMIPP) to identify antecedent ischemia (19,29–32).

Among 111 patients presenting to an ED with acute chest pain who underwent coronary angiography, Kawai et al. (30) reported a sensitivity of BMIPP SPECT imaging of 74% to detect obstructive coronary stenosis or provokable spasm, when BMIPP imaging was performed within 3 days of symptoms. The results of the present study are consistent with those data, generalizing the concept to a larger number of patients studied in multiple centers. In the Kawai et al. (30) study, however, the prevalence of disease was high (as might be expected among a group of patients who underwent angiography). The current study includes a broader range of patients in contemporary practice and uses the final clinical diagnosis of ACS as the truth standard because not all patients underwent angiography on clinical grounds. It is of interest that the sensitivity of BMIPP imaging in the present trial, when assessed based on an angiographic standard in patients with signs of a culprit lesion without collaterals, is ≥90% among several readers.

The sensitivity data reported herein are similar to other data (33) for rest perfusion imaging when MPI was compared with a truth standard using a troponin definition. The current specificity data are also similar to those reported in some of the larger observational series of ED patients studied with rest MPI (6,7). However, it should be noted that the sensitivity of rest MPI is dependent on isotope injection being performed while there is decreased coronary...
flow or a prolonged post-ischemic wall motion abnormality. In clinical studies of MPI for this purpose, patients presenting >3 h after symptom resolution (9), or in some studies >6 h after symptom resolution (6,8), are excluded. The prevalence of perfusion abnormality has been shown to diminish with time after an experimental ischemic insult in an animal model of PCI-induced ischemia (34).

In contrast to these studies, in the present study, patients were included if the isotope could be injected up to 30 h after symptom cessation. This time criterion was based in part on a preliminary study comparing BMIPP imaging with stress-induced ischemia on stress MPI studies (19). From the current data, it is demonstrated that the sensitivity of BMIPP imaging is maintained even many hours after symptom resolution (Fig. 4). This represents a potentially important clinical advantage in that the use of BMIPP imaging may substantially extend the time window within which noninvasive imaging of the effects of ischemia on the myocardium may assist in the evaluation of patients with suspected ACS.

In patients who may present late after symptom cessation, the time course of biomarker elevation would suggest that a single determination many hours after symptom cessation should be sufficient to rule out myocardial necrosis (8) and potentially allow patients to proceed directly to stress perfusion imaging. To the extent that performance characteristics of BMIPP imaging are confirmed in subsequent trials, a single rest BMIPP image to assess for recent ischemia may answer the clinically relevant questions at hand without the need for stress testing. This concept could be tested in future trials.

The choice of a truth standard with which to compare noninvasive tests in the ED setting has been variable in the published literature. Many previous studies of imaging tests in this setting have used MI, often based on a creatine kinase based definition, as the truth standard (6,7). Other studies have used a composite of MI or revascularization (the latter acting as a surrogate for unstable angina) (5,7,8), whereas others have used an angiographic standard of coronary stenosis (26). In the present trial, a truth standard of the final clinical diagnosis of ACS was used to capture the diagnosis for which the imaging is intended and which the evaluating clinician is most interested in ruling in or ruling out. An attempt was made to use all available clinical information out to 30 days of follow-up to inform the adjudication of the truth standard. Nonetheless, ACS remains a clinical syndrome and not a disease per se. In some cases, the

Figure 3 Example of BMIPP SPECT Imaging in a Patient With Suspected ACS

β-methyl-[123I]-iodophenyl-pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT) images from the same patient shown in Figure 2; a large defect is observed with BMIPP in the lateral wall, consistent with the stenosis and the potential culprit lesion seen in the left circumflex coronary artery on the angiogram.
have sufficient information to make a final diagnosis and were prospectively excluded from the analysis of BMIPP performance characteristics.

There are strengths to the analysis. BMIPP imaging was performed in many more centers than had been previously reported in trials, with diagnostic image quality in the vast majority of patients. Image analysis was performed in the rigorous analytic environment consistent with U.S. Food and Drug Administration guidance for analysis of images in clinical trials (35), and quantitative data from a radionuclide- and sex-matched database specific for BMIPP were available to readers.

Conclusions

Imaging fatty acid metabolism with BMIPP SPECT in ED patients with suspected ACS has sensitivity similar to that of other contemporary imaging modalities, although it has the unique property of maintaining sensitivity even when performed up to 30 h after symptom resolution. The addition of BMIPP data to the initially available clinical information adds incremental value for the early diagnosis of an ACS, potentially allowing determination of the presence or absence of an ACS to be made much earlier in the evaluation process.

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