Diagnostic accuracy of β-methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP) imaging: A meta-analysis

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Background. β-Methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP) imaging has been used extensively to detect coronary artery disease (CAD), primarily in Japan. However, the reported sensitivity and specificity vary considerably from study to study. This meta-analysis was conducted to summarize the evidence for the diagnostic accuracy of resting BMIPP imaging in the detection of CAD.

Methods and Results. A MEDLINE search of the literature published through the end of 2006 was performed. Seven studies (528 patients) met the inclusion criteria. Using random-effects models, the overall sensitivity and specificity to detect CAD were 78% (95% confidence interval, 73% to 81%) and 84% (95% confidence interval, 77% to 89%), respectively. A significant threshold effect was identified among studies, which was expected given the between-study variability in study methodology. A summary receiver-operating characteristic curve yielded an asymmetric curve with an area under the curve of 0.91 (SE, 0.020), indicating excellent diagnostic performance.

Conclusions. Imaging with BMIPP at rest exhibits a moderate sensitivity and high specificity to detect CAD in patients with a high prevalence of CAD. Thus, this tracer may be of great value for patients with acute chest pain and those with relative contraindications to exercise or pharmacologic stress myocardial perfusion imaging (MPI). (J Nucl Cardiol 2008;15:345-52.)

Key Words: BMIPP • diagnostic and prognostic application • myocardial ischemia

Under aerobic, fasting conditions, the heart primarily uses fatty acid, because its degradation by β-oxidation yields an abundance of energy-rich phosphates. During ischemia, the myocardium shifts high-energy adenosine triphosphate (ATP) production from fatty acid metabolism to glucose utilization, which can supply ATP through anaerobic glycolysis. The pattern of decreased fatty-acid use and enhanced glucose use is, in fact, the metabolic signature of the ischemic heart.1

β-Methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP) is a methyl branched-chained fatty acid that exhibits prolonged retention (trapping) in the heart because the methyl group inhibits beta-oxidation.2 Defects in BMIPP uptake reflect the decreased fatty-acid metabolism that occurs with ischemia or infarction.3 One considerable advantage of BMIPP imaging is that it is injected under resting condition, and permits the identification of antecedent ischemia.

Although BMIPP has been widely used for more than 10 years, primarily in Japan, the reported sensitivity and specificity to detect coronary artery disease (CAD) vary considerably from study to study, reflecting differences in the process of patient selection, baseline disease severity, and study design. We conducted the present meta-analysis to summarize the evidence for the diagnostic accuracy of resting BMIPP imaging in the detection of CAD.

METHODS

Search Strategy

A review of the literature was performed to identify articles published through the end of 2006 in both the English-language and Japanese-language literature on BMIPP. Articles were obtained through a MEDLINE search using the key word “BMIPP.” The references of the included articles were also examined for additional studies. Japanese-language reports were evaluated by a Japanese author (Y.I.).
Study Eligibility

Articles were included in the analysis if all subjects underwent both BMIPP imaging and coronary angiography, the reference standard for CAD diagnosis. The absolute numbers of true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) were available in the data presented. Both prospective and retrospective studies were included if they met all criteria.

Articles were excluded if they were performed after percutaneous coronary intervention for the assessment of long-term stent patency, if they enrolled fewer than 20 patients, or if they included duplicate data from previous publications. In these cases, only one report was used in the analysis to avoid potentially overlapping data.

Data Extraction

The following information was extracted from each study: first author, year of publication, mean age, number of patients, percentage of male patients, number of patients with documented CAD, percentage of patients with vasospastic angina and previous myocardial infarction (MI), segmental model (number of segments) used for BMIPP imaging, angiographic definition of CAD (75% or 90% luminal-diameter narrowing), and clinical presentation (stable angina, unstable angina, or both).

Statistical Analysis

Statistical pooling. For each study, we calculated sensitivity as TP/(TP + FN), specificity as TN/(TN + FP), the positive likelihood ratio (LR) as (TP/(TP + FN))/(FP/(TN + FP)), the negative LR as (FN/(TP + FN))/(TN/(TN + FP)), and the diagnostic odds ratio (DOR) as (TP/FP)/(FN/TN), with their 95% confidence intervals (CIs). The overall pooling of sensitivity, specificity, the LRs, and the DOR, with 95% CIs, was calculated using a random-effects model.

Threshold analysis. One explanation for the observed differences among studies is their use of different criteria or cutoff points for judging the results of the index test as positive. In this case, the relationship between the true-positive rate (TPR) and the false-positive rate (FPR) is characterized by a tradeoff between sensitivity and specificity, and can be summarized by a receiver operating characteristic (ROC) curve. The TPR and FPR were plotted on the y-axis and x-axis, respectively, and tested for the presence of a threshold effect between studies by calculating a Spearman correlation coefficient.

Testing for heterogeneity. The presence of statistically significant heterogeneity across studies was evaluated by using the \( \chi^2 \) test for heterogeneity. In addition, the effect of heterogeneity was quantified by calculating inconsistency (I²), which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Mild heterogeneity will account for less than 25% of the variation, and significant heterogeneity for more than 50%. Such heterogeneity in a meta-analysis could be the result of variability in thresholds, designs, qualities, and populations among studies. In the presence of significant heterogeneity, pooled summary estimates from meta-analyses are hard to interpret. Sources of heterogeneity were explored by meta-regression analysis.

Summary receiver-operating characteristic. Weighted summary receiver-operating characteristic (SROC) plots, with pertinent areas under the curve (AUCs), were computed using the Moses-Shapiro-Littenberg model. The AUC presents an overall summary of test performance. Perfect tests have AUCs close to 1, whereas poor tests have AUCs close to 0.5. Likewise, the Q* index is another useful global estimate of test accuracy when comparing SROC curves. The Q* index, defined by the point where sensitivity equals specificity on the SROC curve, is the point on the SROC curve that is intersected by the anti-diagonal. A Q* value of 1.0 indicates 100% accuracy (sensitivity and specificity of 100%).

Meta-regression analysis. To determine whether certain study-specific covariates are correlated with test accuracy, a meta-regression analysis was conducted with a weighted least-squares method. The resulting parameter estimates of the covariates can be interpreted, after antilogarithm transformation, as relative DORs (RDORs). They indicate the diagnostic performance of a test in studies with the chosen covariate, relative to its performance in studies without it. If the RDOR is larger than 1, studies with the covariate yield the larger estimates of the DOR than studies without it. Data were analyzed using Meta-Disc (version 1.4) software and STATA 10 (STATA Corp, College Station, Tex).

RESULTS

Overview of Studies

The database searches identified 455 potentially relevant citations (Figure 1). After title and abstract