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BMIPP imaging for assessing myocardial viability in acute and chronic left ventricular dysfunction

P. R. Franken, P. Block

The use of iodine-123-labeled fatty acids is witnessing a resurgence of interest, primarily because of data from recent clinical protocols comparing regional myocardial uptake of 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) with flow tracers (either thallium or sestamibi). Mismatches in BMIPP and flow tracer distribution (BMIPP < flow tracer) reflect the metabolic shift from fatty acid to glucose utilization in ischaemic myocardium. In this sense, the combined imaging of BMIPP and a flow tracer with single photon emission computerized tomography (SPECT) may provide similar and equally important information as fluor-18 deoxyglucose and positron emission tomography regarding the assessment of myocardial viability. The purpose of this article is to review the clinical impact of BMIPP in patients with acute and chronic left ventricular dysfunction for the identification of jeopardized but viable myocardium and for the prediction of functional outcome. *J Clin Bas Cardiol* 1999; 2: 209–12.

Key words: myocardial viability, fatty acids, single photon emission computerized tomography

Noninvasive identification of jeopardized but viable myocardium can be obtained by dobutamine echocardiography and by scintigraphic imaging. Dobutamine echocardiography is an accurate and readily available method [1]. However, it suffers from several limitations including the subjective interpretation of wall motion, the inability to obtain good quality images in a fairly high percentage of patients, and the deleterious effects and even potential risks associated with dobutamine administration. Thallium-201 and technetium-99m sestamibi are myocardial flow tracers showing biological properties that also reflect tissue viability. The probability of viability increases with increasing tracer retention [2, 3]. In the continuum of probabilities, however, a large group of intermediate values exists in between the extremely low and the extremely high. In segments with such intermediate probabilities of viability, the question arises whether metabolic imaging may not discriminate more precisely between viable myocardium and scar tissue.

Positron emission tomography with fluor-18 deoxyglucose (FDG) constitutes currently the gold standard for metabolic imaging although its high cost and limited availability precludes a generalized use. Several iodine-123-labeled fatty acid analogs have been developed to probe myocardial metabolic imaging in vivo using SPECT systems widely available in community hospitals [4]. Among them, iodine-123-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is particularly well suited for SPECT imaging because it demonstrates higher uptake and longer retention in the myocardium [5]. The goal of this article is to review the clinical impact of BMIPP imaging in patients with acute and with chronic left ventricular dysfunction for the identification of jeopardized but viable myocardium and the prediction of functional outcome.

BMIPP retention in normal and ischaemic myocardium

Several experimental studies have reported the metabolism and kinetics of BMIPP in normal and ischaemic myocardium [4–13]. BMIPP is initially delivered by regional blood flow. After transport into the myocyte through a membrane fatty acid-binding protein, most of BMIPP undergoes the adeno-

sine triphosphate (ATP)-dependent activation of the native long chain fatty acids to acyl-coenzyme A. In normal conditions, only a small amount of the extracted BMIPP is backdiffused. The activated BMIPP is then esterised to triglyceride and incorporated in the endogenous lipid pool. The presence of a methyl-group in beta position precludes direct beta-oxidation, although a significant proportion of BMIPP can further be catabolized through alpha-oxidation followed by beta-oxidation. Thus, BMIPP retention mainly reflects the change in lipid pool size in association with the change in fatty acid utilization and not beta-oxidation itself.

In ischaemic myocardium, fatty acid oxidation is suppressed and glucose becomes a major energy substrate for the production of high energy phosphates. BMIPP retention is affected by regional blood flow, a decreased triglyceride pool, and an increased backdiffusion due to reduced ATP content under conditions of ischaemia. The retention of BMIPP has been shown to correlate well with the intracellular ATP levels and with mitochondrial function in ischaemic myocardium. These studies thus indicate that fatty acid metabolism and energy production can be partially assessed by BMIPP despite the limited estimation of the overall energy production.

Discordances between BMIPP and flow tracers may be observed in patients with acute and chronic coronary artery disease [14–19]. Tamaki et al. [20] have shown that in the areas with mismatches in BMIPP and flow tracer distribution (BMIPP < flow tracer), the decreased BMIPP uptake was associated with an increased FDG uptake on PET. The study also demonstrated that the oxidative metabolism in these regions was better preserved than in regions with matched defects. Franken et al. [21] found a significant association between mismatching and contractile reserve assessed by low-dose dobutamine echocardiography in patients with recent myocardial infarction. BMIPP mismatch was observed in all the regions that improved contractility during dobutamine stimulation. In contrast, none of the regions with matched BMIPP and sestamibi defects demonstrated contractile reserve, regardless of the severity of sestamibi defect.

These studies support the concept that regions with less uptake of BMIPP than of flow tracers (perfusion/metabolism mismatch) are likely to correspond to metabolically jeopard-

ized but viable myocardium, whereas regions with concordantly decreased BMIPP and flow tracer (perfusion/metabolism match) are likely to correspond to scar tissue. The presence of thallium or sestamibi may represent restored myocardial perfusion and cell viability, while the reduced BMIPP retention reflects metabolic alterations in both viable and nonviable myocardium. This is the rationale for the combined assessment of BMIPP and flow tracer to identify residual myocardial viability in postischaemic myocardium.

Prediction of functional outcome after acute myocardial infarction

Ito et al. [22] evaluated the ability of BMIPP to predict the recovery of impaired left ventricular function in 37 patients investigated early after emergency coronary reperfusion for acute myocardial infarction. Rest BMIPP and thallium SPECT were performed within a 3-day interval. A severity score was determined from the extent of the imaging defect with each tracer. Left ventricular wall motion score and ejection fraction were obtained at admission and at 1 month after the onset of infarction. The severity score for BMIPP was significantly higher than that of thallium during the acute stage. Left ventricular wall motion and ejection fraction improved at follow-up in the 32 patients showing a significant difference between the severity scores for BMIPP and thallium during the acute stage. By contrast, no change was noted in the other five patients with no difference between the severity scores. In addition, it was demonstrated that the extent of discordant BMIPP retention during the acute stage of infarction was closely related to the extent of recovery of left ventricular wall motion and ejection fraction at follow-up. Thus, early scoring of discordant BMIPP uptake may have predictive value for estimating salvaged myocardium early after coronary reperfusion therapy. The authors concluded that the discordance in the defect size between BMIPP and thallium imaging during the acute stage of infarction is an early predictor of viability of the myocardium at risk of infarction. Similar findings have been reported more recently by Fujiwara et al. [23]. Twenty-three patients with acute myocardial infarction who received direct coronary revascularization underwent both BMIPP and sestamibi SPECT within 2 weeks after onset. Contrast left ventriculography was performed soon after revascularization and repeated 1 month later. Both regional wall motion and left ventricular ejection fraction improved in patients showing discordant tracer retention during the acute stage of infarction.

In another study, Hashimoto et al. [24] used quantitative methods to evaluate the relationship between the discordant retention of BMIPP and thallium early after infarction, and the functional outcome at 3 months after infarction. Fifty-six consecutive patients with acute myocardial infarction were recruited. Thirty-two were treated successfully with emergency coronary revascularization. The remaining 24 patients were treated medically. Reduced myocardial retention of BMIPP and thallium were quantified with a bull's eye technique. Regional wall motion was quantified on a contrast left ventriculogram with a centerline method. The BMIPP severity score was significantly greater than that of thallium at the acute stage of infarction and correlated well with the severity of wall motion abnormalities. During a 2- to 3-month follow-up interval, improvement in regional wall motion abnormality correlated closely with the improved severity scores of BMIPP and thallium in patients treated with emergency coronary revascularization. More importantly, the difference in BMIPP and thallium severity scores at the acute stage of

infarction was significantly related to the recovery from regional wall motion abnormality in patients successfully treated with revascularization but not in patients medically treated.

The incremental value of BMIPP to predict functional outcome after acute myocardial infarction over that provided by either sestamibi alone or by low-dose dobutamine echocardiography was evaluated by Franken et al. [25]. Resting BMIPP and sestamibi SPECT as well as low-dose dobutamine echocardiography were obtained in 18 patients the week following a first acute myocardial infarction. All patients received appropriate treatment according to standard indications, including coronary revascularization in 10 patients. Six months later, all patients underwent a second echocardiographic study to assess functional outcome. Wall motion improved in at least 50 % of the dysfunctional segments in nine patients and was unchanged in the nine other patients. Baseline clinical data, findings on coronary angiography before hospital discharge, and the occurrence and type of revascularization procedure were similar in patients who improved function and in patients who did not. Of the 54 asynergic segments on echocardiography, 61 % showed mismatching with less BMIPP than sestamibi and 39 % matched defects. Wall motion improved in 82 % of the segments with mismatching and was unchanged in 90 % of the segments with matched defects. The overall accuracy of combined BMIPP and sestamibi SPECT in predicting segmental functional outcome was 85 %. These values are similar to those reported with metabolic studies using PET and FDG for differentiating viable from non-viable myocardium. The study also showed that the probability to observe functional improvement in a patient was related to the extent of mismatching. When more than 75 % of the asynergic segments were mismatched, the probability for functional improvement was 90 % (nine of 10 patients). In contrast, none of the 8 patients with less than 75 % of mismatching improved function at follow-up. The sensitivity, specificity and predictive accuracy of combined BMIPP and sestamibi scintigraphy for patient functional improvement 6 months after infarction were 100 %, 89 % and 94 %, respectively. Using as criterion for myocardial viability an arbitrary cutoff of 50 % of the maximal activity, sestamibi uptake alone had a positive predictive value of 84 % and a negative predictive value of 72 %. These figures increased to 95 % and 89 %, respectively, when considering BMIPP (mismatched versus matched defects). Improvement in wall thickening during low-dose dobutamine stimulation had a positive predictive value of 80 % and a negative predictive value of 62 %. These figures increased to 94 % and 94 %, respectively when the relative uptake of BMIPP and sestamibi were considered.

Prognosis and prediction of functional outcome in severe, chronic left ventricular dysfunction

To determine whether BMIPP uptake could also be used to differentiate viable myocardium from scar tissue in patients with chronic left ventricular dysfunction, Hambj e et al. [26] investigated 25 patients with old myocardial infarction. All patients underwent resting BMIPP and sestamibi SPECT and low-dose dobutamine echocardiography within a 3-day period. Among the segments with resting wall motion abnormalities, 16 % showed normal sestamibi and BMIPP, 51 % a mismatching with less BMIPP than sestamibi, 31 % a matched defect, and only 2 % showed a mismatching with more BMIPP than sestamibi. Wall thickening improved under dobutamine stimulation in 54 % of the asynergic segments. A

normal sestamibi was highly predictive for a positive dobutamine response (88 %). However, wall thickening also improved under dobutamine in 63 % of the segments with an abnormal sestamibi uptake. In these segments, BMIPP significantly increased the agreement with dobutamine echocardiography: 58 % of the mismatched segments demonstrated contractile reserve versus only 12 % of the matched segments. The global agreement between the two approaches was 77 %. A normal sestamibi or a mismatching between BMIPP and sestamibi was 72 % predictive for a positive dobutamine response. A matched decrease of both tracers was 88 % predictive for a negative dobutamine response.

To determine the value of BMIPP in predicting functional outcome after coronary revascularization in patients with chronic left ventricular dysfunction, Hambÿe et al. [27] studied 20 patients referred for coronary arteriography because of severe angina pectoris or congestive heart failure. All patients had suffered from at least one Q-wave myocardial infarct between 2 weeks and 15 years before inclusion in the study (median: 3 months). Left ventricular ejection fraction averaged 33 %. Significant coronary artery stenosis was found in an average of 2.1 vessels per patient. Decision to revascularize was based mainly upon technical considerations (quality of the coronary arterial bed, tortuosity, location and number of the lesions). Thirteen patients were revascularized. Follow-up study was obtained 6 months later. All patients demonstrated clinical improvement. Left ventricular ejection fraction increased by 7.3 ± 4.6 % ($p < 0.001$) and end-diastolic volume decreased by 20 ± 28 volume units ($p = 0.03$). Wall thickening improved at follow-up in 62 (58 %) of the 107 asynergic segments which were adequately revascularized. Wall thickening improved in an additional 22 segments (21 %) during dobutamine stimulation. Sestamibi was a poor predictor of functional outcome. The sensitivity, specificity and accuracy to predict functional improvement were only 55 %, 61 % and 56 %, respectively. Adding the BMIPP data significantly improved the accuracy of scintigraphy (90 %) to predict functional outcome after revascularization. Wall thickening improved in 93 % of the asynergic segments showing either normal BMIPP retention or a mismatching with less BMIPP than sestamibi. On the other hand, wall thickening did not improve in 75 % of the segments with a match defect. In addition, the study also demonstrated a significant relationship between the number of mismatched segments and the changes in ejection fraction and volume at follow-up. Moreover, in the seven patients still showing significant mismatching 6 months after revascularization, further increase in ejection fraction was observed at 1 year follow-up.

On the basis of the concept that areas showing less BMIPP retention than flow tracers reflect severe ischaemic and jeopardized myocardium, Tamaki et al. [28] hypothesized that this finding may have prognostic significance. Risk stratification was performed in 50 consecutive patients with chronic myocardial infarction, who were referred to stress thallium imaging and coronary angiography and who underwent BMIPP imaging at rest. Each patient was in a stable condition at the time of the radionuclide study. Follow-up was performed at a mean interval of 23 months to investigate the prognostic implication of the radionuclide studies. Nine patients had cardiac events during the follow-up period. Univariate analysis showed that the number of segments with mismatching was the best predictor of future cardiac events among all the tested clinical, angiographic and radionuclide variables.

Summary and conclusions

The comparison between BMIPP and flow tracers (thallium or sestamibi) allows for the full characterization of the complete spectrum of postischaemic myocardium with SPECT, ie, from complete functional recovery (when the retention of both tracers is normal) to complete transmural necrosis without residual viability (when the retention of both tracers is severely and similarly reduced). Mismatching with more severely depressed fatty acid metabolism than expected on basis of flow is indicative of jeopardized but viable myocardium and is predictive for long term functional recovery. Matched defects are associated with scarring. The additional information provided by BMIPP substantially increases the accuracy of sestamibi alone and of low-dose dobutamine echocardiography in the prediction of functional outcome both in patients with acute and chronic ischaemic left ventricular dysfunction. Although these data remain quite preliminary, perfusion/metabolism mismatch identified with BMIPP and SPECT may play an important role for assessing ischaemic but viable myocardium and risk stratification in patients with coronary artery disease with a similar concept to FDG and PET.

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