stable coronary artery disease and ventricular dysfunction. 


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**Effect of Oral Glucose Loading on the Biodistribution of BMIPP in Normal Volunteers**

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We have evaluated whether myocardial uptake of the fatty acid analog 123I-15-(p-iodophenyl)-3-R,S-methyl pentadecanoic acid (BMIPP) is dependent on the dietary state. **Methods:** We compared the biodistribution of 150 MBq of 123I-BMIPP in six healthy volunteers in two states: after at least 12 hr of fasting and after oral glucose loading (75 g) 60 min before tracer administration, followed by a meal enriched in carbohydrates and protein. Planar and tomographic acquisitions were performed over a 4-hr time period after tracer injection; data were corrected for radioactive decay and injected dose. Radioactivity was measured in blood samples drawn at several points. **Results:** Significant increases of glycemia and insulinemia and a significant drop in plasma nonesterified acids were documented after glucose loading. Half-time values for plasma radioactivity were significantly shorter in the glucose-loaded state than in the fasted state (4.3 ± 1.4 min compared to 6.3 ± 1.3 min, p < 0.05). Activity in the heart and liver tended to be higher in the glucose-loaded state than in the fasted state. SPECT images at 0.5 hr after tracer injection demonstrated that the myocardial wall-to-cavity ratio was higher after glucose than in the fasted state (2.53 ± 0.59 compared to 2.11 ± 0.21, p = 0.15). Washout from the liver between 1 and 4 hr after injection increased from 18.6% ± 4.4% in the fasted study to 24.1% ± 2.4% after glucose (p = 0.04). Washout from the myocardium between 0.5 and 3.5 hr after injection increased from 13.1% ± 8.8% in the fasted study to 24.0% ± 3.7% after glucose (p = 0.05). **Conclusion:** These results indicate that fasting before BMIPP scintigraphy is not mandatory to obtain adequate SPECT images. At the time when SPECT is usually performed, glucose loading may provide improved ratios between myocardial and blood pool activity.

**Key Words:** 15-(p-iodophenyl)-3-R,S-methyl pentadecanoic acid; glucose; biodistribution


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The clinical utility of 123I-labeled 15-(p-iodophenyl)-3-R,S-methyl pentadecanoic acid (BMIPP) in cardiomyopathy as well as in ischemic heart disease has been documented extensively (1,2). In ischemic heart disease, evidence has accumulated that myocardial areas in which the uptake of BMIPP is diminished
relative to perfusion tracers (termed mismatches) are indicative of jeopardized myocardium, which is often dysfunctional (3,4) but is fully capable of recovery (5,6). This stands in contradic-

After an energy-requiring activation, the largest part of BMIPP is subsequently stored in the cytosolic triglyceride pool, because the methyl group in beta position inhibits entry of the activated fatty acid into beta-oxidation (7). However, a small part of BMIPP is metabolized through successive alpha- and beta-oxidation, finally leading to the production of p-iodophenyl-acetic acid (PIPA) (Fig. I) (8,9). BMIPP effectively traces the uptake into the cell and the activation of fatty acids (10,11); indirectly, it reflects cellular adenosine triphosphate content (12).

In analogy to studies with straight-chain analogs, it has become standard practice to perform BMIPP studies after an overnight fast. In contrast to BMIPP, however, straight-chain analogs assess beta-oxidation and, accordingly, should be administered in conditions that favor fatty acid oxidation. The effect of metabolic milieu on the biodistribution of BMIPP in normal volunteers has not been previously addressed. The aim of this study, therefore, was to investigate how metabolic conditions affect the biodistribution of BMIPP and the resulting image quality.

MATERIALS AND METHODS

Study Population

We investigated six healthy male volunteers. Their ages ranged from 19 to 25 yr. Informed consent was obtained, and the study protocol was approved by the institutional ethical review board.

Synthesis of BMIPP

BMIPP was purchased from Emka-Chemie (Markgröningen-Talhausen, Germany) and radioiodinated with 123I(p, n) using a high-yield Cu(I)-assisted radioiodination method described previously (13). This labeling procedure yields 75% 123I-BMIPP, with a radiochemical purity of >97%. The final product had a specific activity of >200 GBq/mmol and was formulated in 6-8 ml of a 4% human serum albumin solution in saline.

Study Protocol

All of the volunteers were imaged twice. The first set of acquisitions was performed after an overnight fast of at least 12 hr. The second time, 1 wk later, the same set of acquisitions was repeated after an oral glucose load of 75 g, followed by a meal enriched in carbohydrates and protein content. This meal contained 70 g of carbohydrates, 41 g of protein and 21 g of fat, for a total of 610 calories, and was consumed 30 min after the glucose load. It was given for the purpose of sustaining the metabolic changes induced by the glucose load for as long as possible (14). Approximately 1 hr before tracer administration, intravenous catheters were placed in each arm, one to be used for tracer injection and the other for blood sampling. For the glucose-loaded study, BMIPP was injected ~1 hr after oral glucose administration.
SPECT Imaging

Acquisition. SPECT of the heart was performed at ~0.5 hr and again at ~3.5 hr after tracer administration. Projection images were acquired into 64 x 64 matrices using a zoom factor of 1.78 in 32 positions of each detector (for a total of 64 projections over 360°) with a dwell time of 60 sec.

Processing. The SPECT studies were reconstructed using a Butterworth filter (order 7, cutoff frequency 0.4 Nyquist), without attenuation correction. Elliptical regions corresponding to the outer and inner contours of the myocardium were drawn on short-axis slices and were used on both the fasted and the glucose-loaded study. Myocardial activity was measured as the total counts between these ellipses, summed over the different slices representing the midventricular and basal regions. Blood activity in the cavity was sampled by the minimal pixel present in this region. Regional activity in the fasted and glucose-loaded state was compared on bull's-eye plots (16). Scores for septal, anterior, lateral and inferior regions were calculated as the mean of the subregions in that area. For the SPECT studies, washout was calculated between 0.5 and 3.5 hr.

Statistical Analysis

Results are expressed as the mean ± s.d. Comparisons between the fasted and glucose-loaded state were made using Wilcoxon's signed rank test or paired Student's t-tests, as appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

Effects of Oral Glucose Load

Figure 3 illustrates the effects of the oral glucose load on plasma glucose, insulin and NEFAs. Glucose and insulin values increased from baseline values (95 ± 10 mg/dl and 12 ± 13 milliunits/liter, respectively) to a peak at the time of tracer injection (134 ± 40 mg/dl and 111 ± 52 milliunits/liter, respectively). Nonesterified fatty acids showed a marked drop (from 0.76 ± 0.41 to 0.08 ± 0.05 mEq/liter), which was sustained from the time of tracer administration over the next 90 min.

Plasma Activity Curves

Figure 4 presents the plasma total activity curves over 20 min (Fig. 4A) and 4 hr after tracer injection (Fig. 4B). The curves for the glucose-loaded state were always below those for the fasted state, although over time, both curves tended to come together. The differences reached statistical significance at 15 and 20 min after tracer injection. Plasma half-times were calculated by simple exponential fitting on the downsloping part of the curves, within 20 min after tracer administration. Half-time was significantly shorter in the glucose-loaded state (4.3 ± 1.4 min) than in the fasted state (6.3 ± 1.3 min, p < 0.05). Figure 4C and D depicts the plasma curves of BMIPP and PIPA. The activity of BMIPP decreased quickly and a slow buildup of PIPA in the plasma took place in both the fasted and the glucose-loaded state. For BMIPP as well as for PIPA, the mean values at all points in time were lower in the glucose-loaded state than in the fasted state, although the difference was not statistically significant.

Time-Activity Curves over the Liver and the Heart

Figure 5 illustrates the mean TACs in regions over the liver (Fig. 5A and B) and heart (Fig. 5C and D). At ~1 hr after tracer administration, activities in the heart were 4.67% ± 0.58%ID in the fasted state and 4.95% ± 0.67%ID in the glucose-loaded state (p = not significant); activities in the liver were 8.80% ± 1.91%ID in the fasted state and 9.57% ± 1.50%ID in the glucose-loaded state (p = not significant). Activity in both liver and heart was higher in the glucose-loaded state than it was in the fasted state, but the differences between both states were markedly less for the heart than for the liver. On the SPECT images, activity in the myocardium was 1.09 ± 0.11 times higher in the glucose-loaded state than in the fasted state (range 0.95–1.24).

Heart-to-Liver and Heart-to-Lung Ratios

Heart-to-liver ratios were significantly lower in the glucose-loaded state than in the fasted state at most time points between 2 and 12 min after tracer administration. Heart-to-lung ratios showed no statistically significant differences between the two
states, except at 4.5 hr after tracer administration, when they were higher after fasting.

**Myocardium-to-Cavity Ratio on SPECT**

Figure 6 shows a typical example of SPECT studies in the fasted and glucose-loaded state in a single volunteer. Blood pool activity in the cavity was lower but myocardial activity was higher in the glucose-loaded state. On planar images, these effects tended to cancel out, which accounts for the small differences observed for the heart TACs between the fasted and glucose-loaded state. Figure 7 illustrates that ratios of activity in the myocardial wall to activity in the cavity tended to be higher (p = 0.15) in the glucose-loaded early SPECT (2.53 ± 0.59) than in the fasted early SPECT (2.11 ± 0.21). On the late SPECT, these differences had disappeared (1.68 ± 0.31 in the fasted state compared with 1.70 ± 0.25 in the glucose-loaded state, p = not significant).

**Regional Myocardial Distribution on SPECT**

The mean distribution of the tracer in the myocardium was not significantly different between the fasted and the glucose-loaded state. The mean scores for the septal, anterior, lateral and inferior wall were 85.9 ± 6.6, 91.4 ± 4.0, 91.1 ± 3.6 and 86.6 ± 7.4 in the fasted state and 87.0 ± 5.6, 89.7 ± 5.6, 92.2 ± 3.2 and 84.6 ± 5.1 in the glucose-loaded state, respectively.

**Initial Washout**

Figure 8 illustrates that washout from the organs during the first hours after injection is increased in the glucose-loaded state. For the liver, washout was higher in the glucose-loaded than in the fasted study (24.1% ± 2.4% compared to 18.6% ± 4.4%, p = 0.04). For the heart, washout was higher in the glucose-loaded study than in the fasted study (14.0% ± 2.8% compared to 10.7% ± 1.8%, p = 0.06). For the myocardium, as isolated on the SPECT images, this difference was even more marked: 24.0% ± 3.7% in the glucose-loaded study compared to 13.1% ± 8.8% in the fasted study (p = 0.05).

**DISCUSSION**

This study demonstrates that dietary state affects the biodistribution of BMIPP only to a minor degree.

**Effect on Plasma Clearance**

BMIPP cleared faster from the plasma in the glucose-loaded state than it did in the fasted state. Faster clearance from the plasma after glucose and insulin infusion has been observed with 1-13C-beta-methylheptadecanoic acid, another methyl-branched fatty acid analog, in mongrel dogs (17). Because plasma clearance is the net result of uptake by the tissues and reflux of substrate or metabolites from the tissues, multiple factors may contribute to enhanced plasma clearance in the glucose-loaded state.

A major factor may relate to the suppressed circulating levels of fatty acids in the glucose-loaded state. Uptake of fatty acids into myocardium is known to display saturation kinetics, with K_m values in the range of 0.24 μmol/g (18). Therefore, decreased competition by fatty acids in the glucose-loaded state might cause higher uptake of the radiolabeled fatty acid into the tissues. To our knowledge, no measurements of the influence of feeding state on forward unidirectional tracer extraction have been published for BMIPP. However, higher one-way extraction of 14-iodophenyl-beta-methyltetradecanoic acid, a fatty
FIGURE 5. Organ TACs. A and B give the mean TACs over the liver, whereas C and D give the mean TACs over the heart. The time frames are the same as those in Figure 3. The ordinate uses the same scale for heart as for liver. *Statistically significant differences.

Acid analog similar to BMIPP, was found in anesthetized greyhound dogs after intravenous infusion of glucose and insulin (0.44 ± 0.06 s.e.m.) than at baseline (0.38 ± 0.06 s.e.m.) (19). Conversely, forward extraction of $^{11}$C-palmitate in mongrel dogs was lower after glucose/insulin infusion (0.38) than in control experiments (0.52) (20). The difference in this respect between palmitate and the methyl-branched tracers BMIPP and 14-iodophenyl-beta-methyltetra-

FIGURE 6. Typical example of early SPECT studies in fasted (A) and glucose-loaded (B) states from a single volunteer. These studies were obtained after injection of the same dose and are normalized to their common maximum. Note the increased myocardium/cavity contrast in the glucose-loaded state.

FIGURE 7. Myocardial wall-to-cavity ratio for the early and late SPECT studies. N.S. = not significant.
tracer administration as calculated on the whole-body images, as well as the
toration, as calculated on the SPECT ¡mages.

washout from the myocardium between 0.5 and 3.5 hr after tracer adminis

FIGURE 8. Washout of activity. The values given are the percentage of
hampers beta-oxidation of the latter compounds.

Second, faster plasma clearance in the glucose-loaded state
may derive from lesser leakage of BMIPP or its metabolites
from the tissues into the plasma, as will be discussed below.

Effect on Metabolism

The lower levels of PIPA in the plasma that we observed in
the glucose-loaded state are testimony to the inhibition of
BMIPP metabolism by glucose. Glucose is known to inhibit
beta-oxidation (21). In the case of BMIPP, such inhibition was
demonstrated in a perfused rat heart model (9).

Effect on Tissue Radioactivity

We found that tissue activity in the liver and myocardium is
higher in the glucose-loaded state. For the heart, this effect
could be appreciated on SPECT images, although the differ-
cences between the fasted and glucose-loaded states did not
reach statistical significance in this small volunteer sample. On
projection images, the effect of increased myocardial activity in
the glucose-loaded state is attenuated because of decreased
activity in the blood.

Increased activity in the heart in the glucose-loaded state is
consistent with the weak positive correlation between myocard-

dial BMIPP uptake and plasma insulin levels and also with the
weak negative correlation between myocardial BMIPP uptake
and serum free fatty acid levels that were observed in 180
patients imaged after fasting (22). Increased activity in the heart
also concurs with the data obtained in perfused rat hearts (9).
At the end of 4 hr of perfusion, the fraction of activity remaining
in the heart was higher after perfusion with glucose and insulin
(55.5 ± 3.0) than after perfusion with oleate (31.6 ± 1.7).
Conversely, from the data provided and by using the kinetic
model described in the paper on L-11C-beta-methylheptadecanoic acid, the tissue plateau concentration reached was
somewhat lower after glucose/insulin infusion than at baseline
in mongrel dogs (17).

Higher tissue activity may result either from increased tracer
extraction or from delayed washout of activity from the tissues.
With respect to the latter, the inhibition of metabolism induced
by glucose and insulin may be important. Indeed, in a dog
model, metabolites derived from alpha- and beta-oxidation
were demonstrated to washout from the myocardium and to
constitute an important fraction of the ID, amounting to 6.6% of
decanoic acid may be caused by the beta-methyl group, which

Intramyocardial Tracer Distribution

Fluorodeoxyglucose (FDG) is more heterogeneously distrib-
uted in the fasted state than in the glucose-loaded state (24).
Because it has been suggested that the heterogeneity of FDG
distribution is based on preferential use of fatty acids by the
septal myocardium (25), we were concerned that the nutritional
state would alter the distribution of BMIPP. However, intr-

tomyocardial distribution proved not to be different between
the fasted and the glucose-loaded state in normal volunteers.
This may derive from the fact that BMIPP does not trace fatty
acid oxidation as such, but rather its uptake into the myocar-
dium.

Tracer Clearance Between One and Four Hours After
Injection

We observed enhanced washout of activity from the myocard-
dium between 1 and 4 hr after injection of 123I-BMIPP after

The lower levels of PIPA in the plasma that we observed in
the glucose-loaded state were testimony to the inhibition of
BMIPP metabolism by glucose. Glucose is known to inhibit
beta-oxidation (21). In the case of BMIPP, such inhibition was
demonstrated in a perfused rat heart model (9).

In this respect, it should be noted that despite the decreased
elevation of 11C-palmitate that these authors found after

Similar enhancement of washout after glucose administration
has been demonstrated in ischemic heart disease (26). This was
explained by accelerated turnover of triglycerides by increased
glycerol-3-phosphate levels induced by glucose. An alternative
explanation may be derived from our data. Immediately after
tracer injection, the influence of glucose on metabolism is still
present. BMIPP is taken up by the tissues and may be activated
and incorporated into cytosolic triglyceride pools, but the
majority is not metabolized through alpha- or beta-oxidation.
As time goes by, however, the metabolic effects of the glucose
load, including the inhibition of fatty acid metabolism induced
by it, decrease. At that point, the excess of BMIPP that has
accumulated in the tissues in the triacylglycerol pool may be
reintroduced into successive alpha- and beta-oxidation, thereby
causing increased washout. Such a release of fatty acid from
complex lipids into the fatty acid utilization pathway has been
demonstrated with 14C-palmitate (27) and the washout kinetics
of 123I-BMIPP has been demonstrated mainly to reflect this
turnover rate of the triglyceride pool in the cytosol (28).

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Clinical Implications

Taken together with the data of Fujimura et al. (26) in ischemic heart disease, our results in healthy volunteers indicate that fasting before BMIPP scintigraphy is not mandatory. To the contrary, at the time when SPECT is usually performed (30 min after tracer injection), glucose loading may provide improved ratios between myocardial and blood pool activity, whereas it does not degrade heart-to-liver or heart-to-lung activity ratios.

CONCLUSION

Our results indicate that fasting before BMIPP scintigraphy is not mandatory to obtain adequate SPECT images. At the time when SPECT is usually performed, glucose loading may provide improved ratios between myocardial and blood pool activity.

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