

BMIPP and Flow Tracers in Myocardial Hypoperfusion

TO THE EDITOR: Reinhardt et al. (1) compared ^{125}I -15-(*p*-iodophenyl)-3-*R,S*-methylpentadecanoic acid (BMIPP) and ^{201}Tl in a rabbit model of myocardial hypoperfusion. They found that both tracers similarly and accurately delineate areas of hypoperfusion distal to a coronary occlusion. These results were compared to those obtained by Nishimura et al. (2) The latter authors used a canine model featuring 3 hr of occlusion followed by 1 hr of reperfusion and observed disparately high BMIPP activity in the reperfused area.

Reinhardt et al. explained the discrepancy by invoking radionuclide crossover in the Nishimura experiment, pointing to the 167-keV photon emitted by ^{201}Tl . However, data analysis as used by Nishimura et al. eliminates this possibility. Indeed, this group used circumferential profiles that were normalized to their maximum (in normally perfused myocardium). The measured relative (compared to a normal area) count rate of thallium was lower than the measured relative count rate of BMIPP. It can be shown mathematically that this can only result when the actual relative activity (i.e., without cross talk) of thallium in the reperfused versus normal segments is lower than the actual relative activity of BMIPP in the reperfused versus the normal area, i.e., when BMIPP is less depressed than thallium in the reperfused areas.

Rather, the results of Nishimura et al. and those of Reinhardt et al. may be reconciled by taking into account differential washout of thallium and BMIPP from the reperfused versus the normal segments. From the description of the experiment by Nishimura et al. it is not clear at which point in time the animals were sacrificed, but this must have been at least 1 hr after BMIPP injection and closer to the injection of thallium. Nishimura found a considerably prolonged half-time of BMIPP washout from the reperfused compared to the normal myocardium. This would attenuate any initial decrease of activity in the reperfused areas. Washout of thallium also will be slower from reperfused than from normal areas, but differential washout may be more marked with BMIPP than with thallium. This was observed in patients with myocardial infarction (3). Moreover, since Nishimura et al. injected BMIPP more than half an hour before thallium, BMIPP had more time to redistribute than thallium. Anyway, long time delays between tracer injection and data acquisition do not correspond to clinical practice, in which images are usually acquired 15 to 30 min after injection of BMIPP (4).

Reinhardt et al. suggest that "the differences observed between the retention of BMIPP and ^{201}Tl may be related to myocardial fatty acid metabolism," because "the initial deposition of BMIPP will, like ^{201}Tl , reflect coronary blood flow in the presence of an acute coronary occlusion." However, since metabolic clearance of BMIPP in ischemic tissue is delayed (2, 3), a finding consistent with observations made on ^{11}C -palmitate (5), mismatches in which BMIPP is less active than perfusion tracers remain unaccounted. Nevertheless, such mismatches are the main finding both in cardiomyopathies and after myocardial infarction (4). The most likely mechanisms involved in such mismatches relate to the determinants of net uptake of fatty acids into the myocardial cell: transport across the cell membrane and subsequent activation. Possible mechanisms, therefore, are either decreased activation of fatty acids, loss of fatty acid binding protein or a combination of both. In normal circumstances, fatty acids are first activated by coenzyme A, before they can enter the mitochondria and beta-oxidation. This activation, by which fatty acids get trapped in the cell, requires ATP. This explains why BMIPP uptake is related to cellular ATP content (6). Activation is inhibited in ischemic, ATP-depleted cells, leading to increased backdiffusion into the blood of BMIPP that has passively entered the cell. Therefore, ischemic cells retain less BMIPP than their normal counterparts. With ^{11}C -palmitate, increased backdiffusion was invoked to explain the lesser extraction of palmitate in ischemic regions. However, it was noted that this lesser extraction was only detectable at quantitative analysis and did not bring about qualitative differences in the images of peak palmitate uptake and those of blood flow

(5). Therefore, it seems unlikely that this mechanism would be able to explain, on its own, the qualitative differences between BMIPP and flow images. The second mechanism that may play a role in the mismatches, then, is loss of fatty acid binding protein, the transport protein mediating the transport of fatty acids into the cells. In ischemic tissue, fatty acid binding protein appears to be released from the cell, reducing the cell's ability to transport fatty acid (7).

In this respect, the findings of Reinhardt et al. may be taken to indicate that during short-time hypoperfusion, these mechanisms for decreased uptake of BMIPP are not (yet) operative, or at least not to a degree detectable in the experiment. It could be worthwhile to repeat their experiments with longer times of hypoperfusion, to delineate more accurately the time intervals over which the decreased uptake of BMIPP occurs.

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REPLY: Dr. De Geeter takes issue with our evaluation of experiments performed by Nishimura (*Eur J Nucl Med* 1989; 15:341-345). Nishimura simultaneously acquired static images of ^{123}I -BMIPP and ^{201}Tl from canine myocardial sections. No correction was made for radionuclide crossover. In our evaluation of this work, we reference a study by our group that evaluates clinical techniques of dual-radionuclide imaging (*J Nucl Cardiol* 1994; 1:39-51). This study clearly demonstrates that "uncorrected" images can be misinterpreted due to Compton scatter and radionuclide crossover artifacts. Therefore, we stated that the results obtained from Nishimura's "uncorrected" images should be interpreted with caution. Moreover, these potential artifacts may help explain the difference between our work and Nishimura's results.

Dr. De Geeter states that data analysis used by Nishimura eliminates potential artifacts because the dataset was normalized to its maximum. Moreover, he states that this fact can be mathematically shown. It is difficult to visualize how normalization of uncorrected data can eliminate Compton scatter and radionuclide crossover artifacts. If this can be mathematically proven, Dr. De Geeter should provide the solution. His discussion of the potential mechanism of BMIPP cardiac transport is another feasible explanation for the differences between our observation and those of Nishimura et al.

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