## Carrier-Mediated Transport of Fatty Acids Causes Mismatch between Measurements of Perfusion and Fatty Acid Metabolism in the Myocardium

**TO THE EDITOR:** The editorial of Knapp (*1*) discusses the mismatch observed between flow tracers and fatty acids labeled with $^{123}I$ in the regional distribution within the heart. In hearts of hypertensive animals, studies of Yonekura et al. (*2*) and Yamamoto et al. (*3*) also demonstrated differences between $^{201}Tl$ and beta-methylated phenylfatty acids (BMIPP) labeled with radioiodine.

The phenomenon of mismatch can be understood on the basis of recent biochemical findings. During pharmacokinetic evaluation of derivatives (*4,5*), strong evidence arose for the hypothesis of a carrier transport system for long chain fatty acids. Stremmel et al. (*6–8*) were able to isolate the carrier, a protein of 40 kDa. A clear dependence of the fatty acid uptake on substrate concentration was observed in human myocardium (*9*) ("saturation kinetics"). The Michaelis-Menten constant $K_M$ and the maximal velocity $V_{max}$ were also determined for the FA transport into the human myocardium; i.e., $K_M$ and $V_{max}$ are 0.24 μmole/g and 0.37 μmole/(g · min), respectively (*10,11*).

For scintigraphic application of fatty acid tracers, the existence of a carrier transport system means that within myocardial tissue the accumulation of the tracer activity depends on perfusion and carrier-mediated transport. Both processes are independent.

Therefore, under conditions of reduced perfusion in the myocardium, the carrier system may still be able to transport a sufficient amount of fatty acid into the myocardial tissue and cover the energy demand. Fatty acid metabolism appears to be normal and a mismatch between flow tracer and radioiodinated fatty acid is found. Another type of mismatch can be observed if the carrier system is disturbed, thereby resulting in reduced uptake of fatty acids, even though the myocardial perfusion is normal.

The uptake of the fatty acid tracer is the product of two factors. A protocol in which $^{201}Tl$ was administered simultaneously with the fatty acid tracer was studied. By dividing the two scintigrams, fatty acid tracer transport is determined as a parametric image (*8,9*). The principle of the procedure can be described schematically by the following equation:

$$\frac{\text{Fatty acid}}{\text{Thallium uptake}} = \frac{[\text{perfusion}][\text{transport}]}{[\text{perfusion}]} \qquad \text{Eq. 1}$$

The details of the mathematics of the schematic Equation 1 have been published previously (*9*).

It is important to note that in vivo human studies demonstrate saturation kinetics characteristic of carrier-mediated processes. Moreover, patients suffering from high blood pressure had "normal" thallium and fatty acid scintigrams, but subsequent analyses clearly showed that fatty acid extraction was reduced by two thirds (*12*).

In summary, we confirm the author's statement that "the factors resulting in the mismatch phenomenon between BMIPP and flow tracers are probably unrelated to the formation of oxidative products." When using fatty acids as myocardial tracers, it has to be realized what question we are asking. Mismatch meant that the actual physiological background was not understood until now, since mismatch is clearly explained by the additional mechanism of a carrier-mediated transport.

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## SPECT in Low-Back Pain: A Wake-up Call

**TO THE EDITOR:** During a recent house move, I thought that I would save some money and move most of the heavy goods on my own with the assistance of one of my colleagues who is a rheumatologist. Both of us forgot that we had passed our respective sell-by dates and ended up having severe low-back pain. After numerous visits to the osteopath and three bottles of analgesics, the pain subsided. Our posture improved from that resembling the hunchback of Notre Dame to that with a slight limp; this was partly aggravated, however, by a bank balance that went into the red.

Since I am a nuclear medicine physician, the possibility of having bone SPECT imaging was tempting. Afterall, with the state-of-art equipment, nothing could stop us from looking at functional images of our skeletons. The powers of MEDLINE were put to test and we cruised the articles and felt confident that we could pinpoint the problem. Then we got the "wake-up call". The recent study by Littenberg et al. (*1*) clearly showed that the use of bone SPECT to evaluate low-back pain was more hype than fact. They recommended well-designed prospective studies to evaluate the role of the technique in low-back pain. The authors must be congratulated for this excellent review. They were polite in their reprimand, but the message was clear and pointed to the sad state of research done by the nuclear medicine community on this subject. The main limitations they found were low patient numbers and vague clinical indications.

The truly depressing point is that a similar state of affairs exists in other aspects of nuclear medicine (excluding cardiology). When skimming through major nuclear medicine journals, it is tempting to argue that this message may apply to other facets of clinical nuclear medicine. It would be extremely useful if the editorial boards of these journals would commission more articles along similar lines that look at other recent indications for scintigraphy. We believe that our clinical colleagues will accept this imaging modality with more enthusiasm and respect if we improve the quality of clinical research.

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## Gallium-67 and Technetium-99m-MDP Scintigraphy for Osseous Involvement in Lymphoma

**TO THE EDITOR:** We read with interest the article by Bar Shalom et al. (*1*). The authors used high-dose $^{67}$Ga and concluded that $^{67}$Ga uptake by $^{67}$Ga-avid lymphoma involving bone may be used to monitor osseous response to treatment (*1*). Moreover, they hypothesized that after effective treatment, $^{67}$Ga scintigraphy will normalize earlier when compared to bone scintigraphy.

We wish to add our experience using low dose $^{67}$Ga, discuss occasional discrepancies using both tracers and present previously unreported false-positive studies.

In a retrospective study of data collected over the last 5 yr, we studied 12 of 87 patients suffering from Hodgkin's (n = 7) or non-Hodgkin's lymphoma (n = 5): 6 men and 6 women; mean age 37 yr; range: 16–66 yr. Inclusion criteria consisted of: (a) $^{67}$Ga avidity of involved lymph nodes, (b) bone involvement confirmed by x-ray and/or CT, (c) availability of $^{67}$Ga and $^{99m}$Tc-MDP bone scintigraphies (mean time interval 7 ± 6 days) before and after treatment with a mean of 4.5 mo follow-up intervals. Gallium whole-body scintigrams were obtained after intravenous injection of 2–4 mCi $^{67}$Ga using a single-headed gamma camera equipped with a medium-energy collimator. For both anterior as well as posterior views, images of 600–800 kcts were collected.

Of the 12 patients, bone involvement was found in one (n = 5), two (n = 4), three (n = 2) and four (n = 1) skeletal sites, respectively. In two patients (A and B), $^{67}$Ga uptake was more intense at one site compared to $^{99m}$Tc-MDP uptake, while in two other patients (C, D) $^{67}$Ga scintigraphy failed to show one site of involvement. In all 12 patients, control $^{67}$Ga scintigraphs were normal, which corresponded with a complete remission as judged by oncological criteria and/or follow-up; however, control bone scintigraphy remained positive.

Contrary to the findings of Orzel et al. (*2*), our data obtained using low-dose $^{67}$Ga confirmed the findings by Bar Shalom et al. (*1*) and their hypothesis that $^{67}$Ga scintigraphy will normalize earlier after effective treatment compared to bone scintigraphy. We suggest that the lower detection rate of $^{67}$Ga scintigraphy compared to $^{99m}$Tc-MDP bone scintigraphy in the series presented by Orzel et al. (*2*) may be due to the use of the bone scan as the gold standard for the detection of lymphomateous osseous involvement rather than to the low dose of $^{67}$Ga injected.

In the article by Bar Shalom et al. (*1*), possible explanations for the occasional discrepancies between $^{67}$Ga and bone scintigraphy were not discussed. In the intermediate and high-grade subgroups of non-Hodgkin's lymphoma patients in whom the sensitivity of $^{67}$Ga scintigraphy for disease detection is high, $^{99m}$Tc-MDP uptake reflecting osteoblastic activity may be low since 77% of bone lesions are lytic. This is illustrated by Patient A in our series and the two patients with bone scintigrams and CT scans in the series by Bar Shalom et al. (*1*). This discrepancy is less likely to occur in Hodgkin's lymphoma since only 14% of bone lesions are lytic (*3*). Gallium-67 scintigraphy may also perform better than $^{99m}$Tc-MDP bone scintigraphy when involvement is limited to bone marrow without osseous invasion. Tumoral heterogeneity (*4*) and overlap between sites of normal $^{67}$Ga uptake, and osseous lymphoma localizations may account for $^{67}$Ga false-negative and $^{99m}$Tc-MDP-positive sites. In our Patient D, involvement of the left maxillary region was not detected on $^{67}$Ga scintigraphy because of overlap of normal $^{67}$Ga uptake in the nasopharyngeal region. This interference could be important in endemic Burkitt's lymphoma in which the most common sites involved are the mandible and maxilla (*5*). Because of the retrospective character of this study, SPECT, which could enable detection of lesions overlapping with sites of normal, uptake was not performed.

In addition to osseous involvement in $^{67}$Ga-avid lymphoma, noninflammatory conditions (*6*), including trauma (*6,7*), untreated Paget's disease (*8*) and osteomyelitis (*9*), may also present as both $^{67}$Ga-and $^{99m}$Tc-MDP-positive bone lesions. In our series, both bone marrow expansion and bone infarction presented as previously unreported scintigraphic imitators of osseous involvement (*10*).


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**REPLY:** We thank Dr. Van de Wiele and his colleagues for their interest in our paper on $^{67}$Ga in lymphoma of the bone (*1*) and appreciate the fact that they had essentially the same results.

We did not hypothesize that $^{67}$Ga will show response to treatment. Rather, we described our findings such that "scintigraphy also correctly monitored bone response to treatment in all but one of the 16 patients." It has been clearly established before that bone scintigraphy is not useful for monitoring response in cancer patients (*2*). Van de Wiele et al. found that $^{67}$Ga scintigraphy correctly monitored response in all 12 patients while bone scintigraphy did not. This is similar to our results.

It is indeed a common, but not a properly studied, belief that $^{67}$Ga is taken up only by high- and intermediate grade-lymphoma. When using high doses of $^{67}$Ga and dual-head high sensitivity cameras with $^{67}$Ga dedicated collimators, however, the sensitivity in most types of low-grade lymphoma is quite similar to that of high- and intermediate-grades. Moreover, SPECT helps in separating normal tissue overlapping lesions and in determining accurate localization of lesion.

None of our patients had bone trauma, Paget's disease or osteomyelitis which, as Van de Wiele et al. correctly state, may take up $^{67}$Ga. In practice, however, the specificity of $^{67}$Ga scintigraphy in lymphoma is high. This is not because $^{67}$Ga is taken up only by lymphoma but because scintigraphy is done only when there is histological proof for lymphoma. The population bias therefore is high.


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