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.

REFERENCES

1. Knapp FF. Myocardial metabolism of radioiodinated BMIPP. *J Nucl Med* 1995;36:1051–1054.
2. Yonekura Y, Brill AB, Som P, et al. Quantitative autoradiographic measurement of regional myocardial substrate utilization in hypertensive rats. *Science* 1985;227:1494–1496.
3. Yamamoto K, Som P, Brill AB, et al. Dual tracer autoradiographic study of beta-methyl-10-[^{14}C] heptadecanoic acid and 15-p-[^{131}I]-iodophenyl-beta-methylpentadecanoic acid in normotensive and hypertensive rats. *J Nucl Med* 1986;27:1178–1183.
4. Machulla HJ, Marsmann M, Dutschka K. Biochemical concept and synthesis of a radioiodinated phenylfatty acid for in vivo metabolic studies of the myocardium. *Eur J Nucl Med* 1980;5:171–173.
5. Machulla HJ, Knust EJ, Vyska K. Radioiodinated fatty acids for cardiological diagnosis. *Appl Radiat Isot* 1986;37:777–788.
6. Stremmel W. Fatty acid uptake by isolated rat heart myocytes represents a carrier mediated transport process. *J Clin Invest* 1988;81:844–852.
7. Goresky CA, Stremmel W, Rose CP, et al. The capillary transport system for free fatty acids in the heart. *Circ Res* 1994;74:1015–1026.
8. Diede HE, Rodilla-Sala E, Gunawan J, et al. Identification and characterization of a monoclonal antibody to the membrane fatty acid binding protein. *Biochim Biophys Acta* 1992;1125:13–20.
9. Vyska K, Machulla HJ, Stremmel W, et al. Regional myocardial free fatty acid extraction in normal and ischemic myocardium. *Circulation* 1988;78:1218–1233.
10. Vyska K, Meyer W, Stremmel W, et al. Fatty acid uptake in normal human myocardium. *Circ Res* 1991;69:857–870.
11. Vyska K, Stremmel W, Meyer W, et al. Effects of temperature and sodium on myocardial and hepatocellular fatty acid uptake. *Circ Res* 1994;74:1–13.
12. Vyska K, Knapp WH, Notohamiprodjo G, et al. Regional myocardial extraction of fatty acids in hypertensive heart disease. *J Hypertens* 1986; 4(suppl 6):S92–S94.

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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.