Letters to the Editor

Measurement of Myocardial Fatty Acid Metabolism by Iodine-123 Heptodecanoic Acid Kinetics

TO THE EDITOR: In their article "Measurement of Myocardial Fatty Acid Metabolism: Kinetics of Iodine-123 Heptadecanoic Acid in Normal Dog Hearts," published in *J Nucl Med* 1986; 28:1449–1455) Schön et al. aim at characterizing the kinetics of omega-^{123}I heptadecanoic acid (IHA) in normal dog myocardium and at relating these kinetics directly to the myocardial oxygen consumption as an index of myocardial oxidative metabolism under different levels of cardiac workload. The paper shows that the kinetics of ^{123}I following the bolus injection of IHA into the coronary artery of open chest dog hearts are different from those of carbon-11 (^{11}C) following injection of the physiologic palmitic acid labeled with ^{11}C, as published elsewhere (*1*). This result is expected and agrees with many observations; it may, however, not be used as an argument against measuring myocardial metabolism with IHA.

Indeed, it has been repeatedly emphasized that it is necessary to correct the gross ^{123}I counts that are obtained after IHA injection from the myocardial region of interest by external measurements, for the contribution from the labeled water soluble catabolites, i.e., mainly inorganic ^{123}I (*2,4*). Also in the studies by Schön et al. the catabolically produced ^{123}I enters the relatively large iodine space in the myocardium and is not as readily removed from the myocardium as is CO_2 that is bound to erythrocytes directly after it enters the capillary bed. The larger the myocardial mass, the lower the heart rate, the more extensive the microcirculation and the surface area-permeability product for iodine exchange into tissue. On the other hand, the transit of water soluble ^{123}I from the mitochondria to the blood circulation in the myocardium is relatively rapid; its value was measured ~2 min, and it was less than 1 minute for CO_2 (*5*). Comparable data were obtained in mice (*6,7*); because of principle similarities in histology and function in mammalian myocardium, this transit time should be similar in different mammals (*7*).

Throughout their work Schön et al. fail to consider the difference between the kinetics of IHA and of water soluble ^{123}I; in fact, this lack of consideration was the reason for previous failures of measuring myocardial lipid metabolism from gross counts of ^{123}I after i.v. injection of omega-^{123}I-hexadecanoic acid that in general behaves similarly to IHA (*8*). For solving this problem, the dual tracer analysis was introduced in order to subtract from the gross ^{123}I counts the signals that originate in the decay of water soluble ^{123}I in the myocardium (*4*). After proper separation of the kinetics of water soluble ^{123}I from the gross counts of ^{123}I, the resulting time-activity curve relates to IHA and its lipid conjugates (*5*); also in man the corrected IHA curve is practically the same as that obtained with [^{11}C]palmitic acid (*9*) and both respond comparably to metabolic interventions (*10,11,12*).

Thus, the measurements by Schön et al. do not permit any conclusion relating to the turnover of myocardial lipids, so that the claim of the authors that IHA cannot be used for measuring myocardial metabolism from the half-time or clearance rates of tracer is in no way supported by their data.

References

1. Schön HR, Schelbert HR, Robinson G, et al. C-11 labeled palmitic acid for the non-invasive evaluation of regional myocardial fatty acid metabolism with positron-computed tomography. *Am Heart J* 1982; 103:532–547.
2. Freundlieb Chr, Hoeck A, Vyska K, et al. Nuklearmedizinische Analyse des Fettsäureumsatzes im Myokard. In: Oeff K, Schmidt HAE, eds. Nuklearmedizin—Nuklearmedizin und Biokybernetik (14th International Annual Conference Society Nuclear Medicine, Berlin, 1976), Stuttgart-New York: F.K.-Schattauer Verlag, 1978: 415–419.
3. Freundlieb Chr, Hoeck A, Vyska K, et al. Myocardial imaging and metabolic studies with (17-I-123)iodoheptadecanoic acid. *J Nucl Med* 1980; 21:1043–1050.
4. Feinendegen LE, Vyska K, Freundlieb C, et al. Non-invasive analysis of metabolic reactions in body tissues, the case of myocardial fatty acids. *Eur J Nucl Med* 1981; 6:191–200.
5. Beckurts TE, Shreeve WW, Schieren R, et al. Kinetics of different 123-I- and 14-C-labelled fatty acids in normal and diabetic rat myocardium in vivo. *Nucl Med Commun* 1985; 6:415–424.
6. Machulla HJ, Stoecklin G, Kupfernagel C, et al. Comparative evaluation of fatty acids labeled with C-11, Cl-34m, Br-77 and I-123 for metabolic studies of the myocardium: concise communication. *J Nucl Med* 1978; 19:298–302.
7. Feinendegen LE, Shreeve WW. On behalf of I-123 fatty acids for myocardial metabolic imaging. *J Nucl Med* 1983; 24:545–546.
8. Poe ND, Robinson GD, Graham LS, et al. Experimental basis for myocardial imaging with 123-I-labeled hexadecanoic acid. *J Nucl Med* 1976; 17:1077–1082.
9. Notohamiprodjo G, Schmid A, Spohr G, et al. Comparison of myocardial metabolism of 11-C-palmitic acid and 123-I-heptadecanoic acid in man [Abstract]. *Eur J Nucl Med* 1984; 9:A26.
10. Notohamiprodjo G, Schmid A, Spohr G, et al. Comparison of myocardial metabolism of 11-C-palmitic acid (11-CPA) and 123-I-heptadecanoic acid (123-IHA) in man. In: Schmidt HAE, Vauramo DE, eds. Nuklearmedizin—Nuklearmedizin in Forschung und Praxis. Stuttgart-New York: F.K. Schattauer Verlag, 1984: 233–236.
11. Dudczak R, Kletter K, Frischauf H, et al. The use of 123-I-labeled heptadecanoic acid (HDA) as metabolic tracer. Preliminary report. *Eur J Nucl Med* 1984; 9:81–85.
12. Schelbert HR, Schwaiger, M. PET studies of the heart. In: Phelps M. Mazziotta J, Schelbert H, eds. Positron emission tomography: principles and applications for the brain and the heart. New York: Raven Press, 1986:581–661.

L. E. Feinendegen
Institut für Medizin
der Kernforschungsanlage Jülich GmbH
Jülich 1, West Germany

REPLY: In response to the letter of Dr. Feinendegen regarding our article, it is well appreciated that the gross iodine-123 (^{123}I) counts of an externally recorded time-activity curve have to be corrected for the contribution of free ^{123}I, however, only for intravenous administration of [^{123}I]heptadecanoic acid

(IHA). The references Dr. Feinendegen quotes in this respect (Ref. *2–4*) deal with intravenous injection of IHA. In our experiments, however, the intracoronary bolus injection technique of IHA was used. This approach, validated in numerous studies (*1–7*) for the investigation of tracer kinetics of the heart, minimizes the effects of tracer recirculation on the primary myocardial time-activity curve and permits visual and quantitative analysis of the intrinsic turnover of tracer substances in myocardium. Similar to all the above cited studies using intracoronary injections, in our experiments the arterial concentration of radioactivity after injection was negligible; 1 min after intracoronary bolus injection of IHA it measured 10^{-3} of peak activity with a further exponential decrease. Hence, there was no need to consider the 'difference between the kinetics of IHA and of water soluble ^{123}I' as pointed out by Dr. Feinendegen.

There is no inverse relationship between myocardial mass and heart rate (*8*) or heart rate and microcirculation (*9*). In fact, in a normal heart myocardial blood flow increases with an increase in heart rate (*9*). As the surface area-permeability product is dependent on flow (*10*), it does not increase with reduced heart rate.

The metabolic fate of free fatty acids (FFA) in myocardium is oxidation. In other words, measurement of myocardial FFA metabolism means primarily measurement of FFA oxidation. It was previously demonstrated that following intracoronary injection of carbon-11 (^{11}C) palmitic acid (CPA), the myocardial clearance rate of the early phase of the ^{11}C time-activity curve was closely related to myocardial oxygen consumption (MVO_2) and $^{11}CO_2$ production as the end product of CPA oxidation (*4*). Since this relationship to MVO_2 could not be detected in our IHA experiments under similar experimental conditions, it is justified to conclude that the half-time of the early phase of the IHA time-activity curve does not provide quantitative information about IHA oxidation as catabolically produced ^{123}I is released from myocardium with an increase over time. The actual clearance rate of the early phase is the rate of myocardial ^{123}I release, which according to our findings could be identified as release of IHA and free ^{123}I. Since this rate is not inversely related to myocardial oxidative metabolism, how could it be a measure of myocardial FFA metabolism?

It is not correct to conclude from similar myocardial time-activity curves to similar tracer kinetics, as shown in our experiments with IHA and CPA. Furthermore, interventions with respect to altered MVO_2 have not been performed for both tracers by other investigators yet. It may be pointed out, that Ref. 12 in Dr. Feinendegen's letter does not deal with metabolic interventions of IHA at all. In fact, these authors state that omega-halogenated fatty acids 'still lack information on their tissue kinetics in relation to FFA metabolism' (*11*).

Our results indicate that the ^{123}I clearance rate during the early phase does not provide any quantitative information about myocardial IHA oxidation. However, it was pointed out in our conclusion, that the ratio between the size of the early and late phase might give qualitative information about regional myocardial IHA metabolism.

References

1. Metzger JM. Myocardial blood flow and oxygen consumption using $H_2{}^{15}O$ and ^{15}O-hemoglobin. Ph.D. Thesis, Washington University, St. Louis, Missouri, 1972.
2. Poe ND. Comparative myocardial uptake and clearance characteristics of potassium and cesium. *J Nucl Med* 1972; 13:557.
3. Schelbert HR, Phelps ME, Hoffman EJ, et al. Regional myocardial perfusion assessed with N-13 labeled ammonia and positron emission computerized axial tomography. *Am J Cardiol* 1979; 43:209.
4. Schön HR, Schelbert HR, Robinson G, et al. C-11 palmitic acid for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron-computed tomography. I. Kinetics of C-11 palmitic acid in normal myocardium. *Am Heart J* 1982; 103:532.
5. Schön HR, Schelbert HR, Najafi A, et al. II. Kinetics of C-11 palmitic acid in acutely ischemic myocardium. *Am Heart J* 1982; 103:548.
6. Visser FC, Eenige van MJ, van der Wall EE, et al. The elimination rate of 123-I heptadecanoic acid after intracoronary and intravenous administration. *Eur J Nucl Med* 1985; 11:114.
7. Schön HR, Senekowitsch R, Berg D, et al. Measurement of myocardial fatty acid metabolism: kinetics of iodine-123 heptadecanoic acid in normal dog hearts. *J Nucl Med* 1986; 27:1449.
8. Braunwald E. Assessment of cardiac performance. In: Braunwald E, ed. Heart disease. Philadelphia: W.B. Saunders Co., 1980: 472.
9. Sheffield LT. Exercise stress testing. In: Braunwald E, ed. Heart disease. Philadelphia: W.B. Saunders Co., 1980: 253.
10. Phelps ME, Huang SC, Kuhl DE, et al. Cerebral extraction of N-13 ammonia: its dependence on cerebral blood flow and capillary permeability-surface area product. *Stroke* 1981; 12:607.
11. Schelbert HR, Schwaiger M. PET studies of the heart. In: Phelps M. Mazziotta J, Schelbert H, eds. Positron emission tomography: principles and applications for the brain and the heart. New York: Raven Press, 1986:581.

Hans R. Schön
I. Medizinische Klinik
und Poliklinik rechts
der Isar der Technischen
Universität München
West Germany

Measurement of Myocardial Fatty Acid Metabolism by Iodine-123 Heptadecanoic Acid Kinetics

TO THE EDITOR: Recently Schön et al. (*1*) reported the limitations of the use of iodine-123 heptadecanoic acid (IHA) kinetics as a probe for myocardial fatty acid metabolism. Based on their experiments in dogs they concluded that IHA kinetics do not correlate quantitatively with beta-oxidation; however they qualitatively correlate changes of myocardial fatty acid metabolism with the component ratio—the ratio of the size of the early and late phase of IHA turnover, but not with their phase half-lives. Although I am pleased that this experimental study (*1*) confirm the conclusions that we have drawn of the clinical usefulness of assessing component ratio from a clinical IHA-study under resting conditions in 60 humans with different cardiac diseases (*2*), a further comment on the conclusions of Schön et al. (*1*) seems indicated.

In their final statement the authors express the opinion that