Measurement of myocardial utilization of long chain fatty acids using omega-labeled radioanalogs

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The isolated perfused working rat heart allowed evaluation of $\sp{125}$I-labeled 16-iodohexadecanoic acid (IHDA), 15-p-iodophenylpentadecanoic acid (βMe-IPPA) and $\sp{18}$F-labeled 16-fluorohexadecanoic acid (FHDA) as indicators of long chain fatty acid (LCFA) oxidation in nuclear medicine studies. Myocardial kinetics and radioanalysis of tissue and coronary effluent showed response of tracers in normal and impaired fatty acid oxidation states. The carnitine palmitoyltransferase I inhibitor (CPT-I; EC 2.3.1.7), 2 (5(4-chlorophenyl)pentyl) oxirane-2-carboxylate (POCA), effected a 90% reduction of palmitate oxidation without significant loss of hemodynamic performance or coronary flow in working hearts perfused with glucose and palmitate. For IHDA and IPPA in control hearts, early myocardial clearance kinetics were rate-limited by the diffusion of primary catabolites, iodide and iodobenzoic acid, respectively. Decreased fatty acid oxidation in POCA treated hearts was indicated in IHDA and IPPA residue curves by a decrease in the relative size of the early clearance component. IPPA showed less back-diffusion of non-oxidized tracer than IHDA; this discrepancy was most apparent in POCA hearts. In vitro binding assays suggested higher tissue:albumin relative affinity for IPPA than for IHDA. Thus, IPPA early clearance kinetics were more closely related to the clearance of labeled catabolite(s) and were therefore more sensitive to the oxidation rate of LCFA. βMe-IPPA kinetics were insensitive to changes in fatty acid oxidation rate and net utilization of LCFA. The methylated fatty acid was readily incorporated into complex lipids but poor substrate for oxidation. POCA did not significantly alter metabolism of the tracer, suggesting that the tracer is poorly metabolized beyond βMe-IPPA-CoA in the oxidative pathway. Myocardial kinetics of FHDA were found to be similar to those of IHDA. However, more rapid early clearance evidenced faster diffusion of the primary labeled catabolite, fluoride, than that of iodide. A compartmental model including non-esterified tracer, catabolite, and complex lipid compartments within tissue successfully fit IPPA residue curves and delineated impairment of LCFA oxidation in hearts by POCA. This technique allowed estimation of the oxidized fraction of the tracer and may be suitable for extension to in vivo measurements with positron tomography and appropriate modified fatty acids.