Monocationic radiotracer kinetics and myocardial infarct size: a perfused rat heart study

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Abstract

Objective To compare the myocardial kinetics of three 99mtechnetium-labeled monocationic tracers [methoxyisobutylisonitrile (MIBI), tetrofosmin, and Q12] in a model of ischemia–reperfusion (IR) to determine their abilities to assess myocardial viability.

Methods Isolated perfused rat hearts (n = 30) were studied in control and IR groups for each tracer. IR hearts were treated with 120 min global no-flow followed by 5 min reflow, then 60 min tracer uptake/clearance. Tracer kinetics were monitored using a scintillation detector.

Results This model produced significant myocardial injury, without significant differences in the percentage of injured myocardium by triphenyltetrazolium chloride (TTC) staining and creatine kinase (CK) assay. Transmission electron microscopy analysis also confirmed necrosis with abundant mitochondrial damage in the IR hearts. All three IR groups exhibited significantly less mean (±standard error of the mean) tracer retention than matched controls (MIBI 73.4 ± 4.9% vs. 96.9 ± 1.76%, tetrofosmin 38.7 ± 4.6% vs. 82.2 ± 3.5%, and Q12 23.0 ± 2.5% vs. 43.8 ± 1.8%, respectively; P < 0.05). Tetrofosmin IR hearts exhibited 54 ± 9% of control myocardial retention, which was significantly less than either MIBI (86 ± 5%, P < 0.05) or Q12 (63 ± 6%, P < 0.05); thus, tetrofosmin provided the best differentiation between nonviable and normal myocardium. Furthermore, tetrofosmin end activity (%id/g) in controls was significantly higher than Q12 (4.09 ± 0.04 vs. 1.71 ± 0.06, respectively, P < 0.05), and tetrofosmin end activity (%id/g) in IR hearts was significantly higher than Q12 (2.19 ± 0.37 vs. 1.06 ± 0.12, respectively, P < 0.05). The correlation between end activity and viable myocardium determined by TTC staining was r = 0.66 (P < 0.05) for MIBI, r = 0.94 (P < 0.05) for tetrofosmin, and r = 0.91 (P < 0.05) for Q12. The correlation between myocardial end activity and myocardial CK leak was r = −0.62 (P < 0.05) for MIBI, r = −0.87 (P < 0.05) for tetrofosmin, and r = −0.89 (P < 0.05) for Q12.

Conclusions Nonviable myocardium can be distinguished from normal myocardium by the retention kinetics of all three monocationic tracers studied. Tetrofosmin and Q12 end activities demonstrate the best correlation with infarct size. However, tetrofosmin kinetics may combine the greatest differentiation between nonviable and normal myocardium, while still retaining adequate activity for imaging.

Keywords 99mTechnetium · Perfusion imaging agents · Myocardial viability · Ischemia · Reperfusion

Introduction

Noninvasive detection of viable myocardium is clinically important in identifying patients who would
benefit most from revascularization, and in evaluating the efficacy of revascularization. 201Thallium (Tl) imaging has been used previously because it exhibits delayed redistribution into viable myocardium. However, the absence of 201Tl redistribution does not absolutely exclude viability, and reinjection of tracer with additional delayed imaging is often required to detect viability [1, 2]. Three 99mTc-labeled monocationic myocardial imaging agents, 99mTc-sestamibi (methoxyisobutylisonitrile, MIBI), 99mTc-tetrofosmin, and 99mTc-furifosmin (Q12), have been proposed for the assessment of myocardial viability [3–6]. These agents offer physical advantages over 201Tl and share the properties of lipophilicity, small molecular size, and monocationic charge. They share similar mechanisms of cellular uptake which are in large measure driven by electrical transmembrane potential differences. In normal myocytes, monocationic agents localize primarily in mitochondria and less in the cytosol. Because of the common mechanism of myocardial retention, which involves intact mitochondrial membrane potential differences, MIBI, tetrofosmin, and Q12 may be useful in identification of viable myocardium even though their utility as viability markers remains controversial in both basic and clinical literature [7]. Furthermore, no studies have compared the kinetic properties of these three 99mTc-labeled monocationic agents in an identical model of severe myocardial injury. Accordingly, the objective of this study was to compare the kinetics of these three monocationic tracers (MIBI, tetrofosmin, and Q12) in a well-established, well-controlled model of severe injury owing to ischemia-reperfusion (IR), to determine the extent to which each can provide an accurate assessment of myocardial viability.

### Methods

#### Animals and isolated perfused rat heart preparation

Thirty male Sprague–Dawley rats (350–400 g) were used for these experiments. The isolated perfused rat heart model was established using a modified Langendorff preparation which has been described earlier [8]. In brief, hearts were isolated and perfused in a retrograde manner at a normal flow rate (12 ml/min) with a modified Krebs–Henseleit solution, containing (mMol/l) 1.25 KH₂PO₄, 0.56 MgSO₄, 1.51 CaCl₂, 4.88 KCl, 0.833 EDTA, 127 NaCl, 20 NaHCO₃, and 5.77 C₆H₁₂O₆. The solution was bubbled continuously with 95% O₂/5% CO₂ to maintain 250% O₂ saturation and pH between 7.35 and 7.45. To monitor left ventricular pressure (diastolic and systolic pressure), a latex fluid-filled balloon connected to a stiff catheter was inserted through the left atrium into the left ventricle. The catheter was connected to a Statham P23ID pressure transducer. Left ventricular end-diastolic pressure was established at 5–10 mmHg by adjusting the balloon volume prior to baseline measurements. Left ventricular developed pressure was equal to systolic pressure minus diastolic pressure. Coronary perfusion pressure (CPP) was monitored throughout each experiment using a similar pressure transducer connected to the perfusion line above the heart. The heart rate was maintained at 300 beats per minute by atrial pacing throughout the protocol. A computerized physiological recorder was used to monitor hemodynamic data.

#### Groups and protocol

Two groups were studied for each of the three tracers: control (n = 5 x 3) and IR (n = 5 x 3). All isolated hearts were perfused for 20 min during baseline to stabilize hemodynamic parameters. Following baseline, IR hearts were subjected to treatment consisting of 120 min global no-flow and 5 min reflow to allow stabilization of hemodynamic parameters post-reperfusion. A total of 5.55 mBq (150 μCi) 99mTc-labeled MIBI, tetrofosmin, or Q12 were then administered to the IR hearts in Krebs–Henseleit solution over 1 h following stabilization. Control hearts received no treatment after 20 min baseline, and then received administration of a 99mTc-labeled tracer for 1 h.

#### Radiotracer delivery

Methoxyisobutylisonitrile (Cardinal Health Dublin, OH, USA), tetrofosmin (GE Healthcare Dallas, TX, USA), and Q12 (Mallinckrodt Medical, Saint Louis, MO, USA) were radiolabeled with 99mTc according to instructions accompanying the kits from respective manufacturers. The labeling efficiency was always greater than 95%. Radiotracer delivery was achieved using a computer-controlled pump (Harvard Apparatus, Natick, MA, USA), which was connected to the perfusion line just above the heart. The pump was programmed to deliver each tracer according to published blood clearance data for that tracer, which simulated tracer recirculation in a single-pass model [6, 9, 10]. The equations for the blood clearance curves were: MIBI Y = 13.49*exp(−X/95.26) + 53.52*exp(−X/2.18) + 33.58*exp(−X/2.19), tetrofosmin Y = 41.57*exp(−X/95.83) + 38.63*exp(−X/15.77) + 20.43*exp(−X/15.76), and Q12 Y = 14.54*exp(−X/62.86) + 70.95*exp(−X/6.03) + 14.51*exp(−X/0.55). The blood time–activity curves are shown in Fig. 1. The speed of the pump delivering...