

Technetium-99m Labeled Fatty Acid Analogues for SPECT Imaging in Heart and Liver

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Abstract

Fatty acid imaging can measure fatty acid oxidation rates in heart or liver for research applications in animals and clinical applications in humans with metabolic disorders. Recent advances in fatty acid imaging using single photon emission computed tomography (SPECT) include the wide applications of the tracer beta-methyl-p-[¹²³I]-iodophenyl-pentadecanoic acid (BMIPP) to assess ischemic heart disease, cardiomyopathies, myocarditis, acute coronary syndrome, and heart failure and the design of new technetium-99m labeled tracers. In this mini-review article, several technetium-99m labeled fatty acid analogues as SPECT tracers are characterised, and the uptake of tracers, clearance from tissues, and mechanism of metabolism are discussed in detail. We subsequently summarized that some essential modification in fatty acid analogue structure can exert profound differences in the biodisposition and specificity of these tracers to improve the uptakes of fatty acids and prolong their retention in myocardium/hepatocyte. Thus, technetium-99m labeled fatty acid analogues have significant potential to play an important role as clinical SPECT traces of fatty acid oxidation in cardiovascular diseases, liver, and other applications in skeletal muscle and tumors.

Keywords: SPECT; Technetium-99m; Fatty acid; Beta-oxidation; Fatty acid oxidation; BMIPP

Introduction

Fatty acids are important substrates for energy metabolism under aerobic conditions, particularly in the heart, liver, skeletal muscle, tumors and so on [1-3]. After uptake by the tissues, fatty acids enter mitochondrial beta-oxidation by removing two-carbon units or are incorporated into the triglyceride pool [4,5]. In the myocardium, more than 80% of fatty acids uptake is directly oxidized and only a small fraction is stored as triglycerides after fasting [5,6]. Whereas in liver, medium chain fatty acids more easily enter the mitochondria without the use of carnitine shuttle system and are predominantly metabolized via beta-oxidation [7]. Energy metabolic pathways in heart and liver are sensitively regulated and immediately reflect any pathological changes or abnormalities. So monitoring of Fatty acids metabolism provides substantial information about the disease state and therapeutic progress. Therefore, the beta-oxidation of fatty acid can be a marker for energy metabolism of the heart and liver. For past decades, fatty acids were radiolabeled with various radionuclides to evaluate fatty acid metabolism using single photon emission computed tomography (SPECT) and positron emission tomography (PET), which can provide an easy visualization of tissues energy metabolism in a noninvasive and quantitative manner.

The currently available tracers for metabolic imaging comprise several fatty acid tracers, ¹⁸Ffluorodeoxyglucose (FDG) for the evaluation of glucose metabolism and ¹¹C-acetate for the assessment of oxygen consumption [4]. Of these tracers, only ¹²³I-labelled fatty acid-based SPECT tracers are currently in routine practice in some of the European countries and Japan, but not in other countries [4,8]. As long chain fatty acid PET radiotracer, 1-[¹¹C]Palmitate showed short physical half-life (20.4 min) and biexponential clearance in heart with rapid washout via beta-oxidation and slow turnover of triglycerides [9]. In addition, the quantitation of the dynamic PET images is not possible in ischemic myocardium because of the rapid diffusion rates of the oxidation product ¹¹CO₂ and unoxidized ¹¹C-palmitate, thereby confounding the model fit [10,11]. 16-[¹⁸F]Fluoropalmitic acid (FPA) showed a same initial myocardial uptake and a longer retention than 1-[¹¹C]Palmitate. 14-[¹⁸F]Fluoro-6-thiaheptadecanoic acid (FTHA) and 18-[¹⁸F]fluoro-4-thia-oleate (FTO), ¹⁸F-labeled thia fatty acids as

metabolically trapped tracers of fatty acid oxidation, were designed for prolonged myocardial retention [8]. Nevertheless, FTHA is the most-investigated thia fatty acid PET tracer in clinical trials in heart [12], liver [1,13], skeletal muscle [2], tumor [3], and brain [14]. However, short half-life of ¹⁸F (110 min) and rapid washout of those tracers in heart were unfavourable for clinical diagnosis. Thus, the lack of ¹⁸F/¹¹C-labeled fatty acid-based PET tracers motivated further tracer development to improve myocardial uptake and retention. Fatty acid imaging has a long history, with iodinated fatty acids being labeled in the 1960s for heart imaging [15]. Among those tracers, 15-(p-[¹²³I]iodophenyl)-3-methylpentadecanoic acid (BMIPP) [16] has been studied extensively in clinical settings as well as in animal experiments. This compound is designed for SPECT imaging, which requires long myocardial retention of the tracer for good image quality [4]. However, the high cost of the accelerator-produced radionuclide iodine-123 and the nuclear properties of shedding radioiodine have constrained the application of those tracers. A Tc-99m-labeled fatty acid analogue would be highly desirable because of the ideal nuclear properties of this radionuclide (141 keV, *t*_{1/2} = 6 h) and its easy availability through the ⁹⁹Mo/^{99m}Tc generator system whenever needed.

In the past decades, various Tc-99m complexes incorporating fatty acid analogues have been developed, but no compound has potential use in clinical practice for poor myocardial uptake and rapid washout from heart. Recently, [^{99m}Tc]-MAMA-hexadecanoic acid (^{99m}Tc-MAMA-HDA), [17] [^{99m}Tc](CO)₃-15-[N-(acetyloxy)-

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2-picolylamino]pentadecanoic acid (^{99m}Tc -PA-PA), [18] [^{99m}Tc] cyclopentadienyltricarbonyltechnetium pentadecanoic acid (^{99m}Tc -CpTT-PA) [19] and 16-cyclopentadienyl tricarbonyl technetium-99m 16-oxo-hexadecanoic acid (^{99m}Tc -CpTT-16-oxo-HDA) [20] showed higher initial heart uptakes than early ^{99m}Tc -labelled fatty acid analogues, such as ^{99m}Tc -BAT-pentadecanoic acid, ^{99m}Tc -labelled DTPA or EDTA fatty acids [21,22]. Those Tc-99m-labeled fatty acid analogues were analyzed using the metabolites in rodent heart or urine samples to elucidate whether those analogues are recognized and metabolized by heart via beta-oxidation. ^{99m}Tc -MAMA-HDA, ^{99m}Tc -PA-PA, ^{99m}Tc -CpTT-PA and ^{99m}Tc -CpTT-16-oxo-HDA were primarily metabolized to ^{99m}Tc -MAMA-butyric acid, $^{99m}\text{Tc}(\text{CO})_3$ -[N-(acetyloxy)-2-picolylamino]pentanoic acid, ^{99m}Tc -CpTT-propionic acid and ^{99m}Tc -CpTT-4-oxo-butyric acid via beta-oxidation in myocardium, respectively. All those tracers were developed with long linear chains fatty acids incorporating various ^{99m}Tc -labeled bifunctional chelating groups [23], which showed different accumulation and rapid washout of the tracers in heart or liver. However, a good quality of ^{99m}Tc -labeled fatty acid-based SPCT imaging requires that the structure modification of fatty acid should conform to its natural properties and the metabolism mechanism in heart, liver and other tissues. In this mini-review, we intend to introduce the incremental development and highlight promises of ^{99m}Tc -labeled fatty acids as potential tracer for fatty acid oxidation imaging in heart and liver.

^{99m}Tc -MAMA-fatty Acid Analogues

Development of a ^{99m}Tc -labeled fatty acid analogue is of interest, as ^{99m}Tc is logistically advantageous over the cyclotron-produced ^{11}C and ^{123}I . [^{99m}Tc]-MAMA-hexanoic acid (^{99m}Tc -MAMA-HA) (Figure 1a) was the first ^{99m}Tc -labeled MAMA medium-chain fatty acid analogues that reflected beta-oxidation activity of the liver in rats [24]. After intravenous administration of ^{99m}Tc -MAMA-HA, the tracer showed high initial accumulation in the liver followed by clearance of the radioactivity in the urine. On the basis of these findings, [^{99m}Tc]-MAMA-dodecanoic acid (^{99m}Tc -MAMA-DA) and ^{99m}Tc -MAMA-HDA (Figure 1a) were prepared using the MAMA ligand incorporating the omega-position of long-chain fatty acid analogues as a chelating group for technetium-99m that reflected beta-oxidation of fatty acid in the heart [17]. In biodistribution studies, ^{99m}Tc -MAMA-HDA showed a high initial uptake followed by a rapid clearance from the heart of normal rats. The maximum heart to blood ratio was 3.6 at 2 min postinjection (pi) of ^{99m}Tc -MAMA-HDA, which was almost half the value of that of [^{125}I]-IPPA. The kinetics of the clearance of

radioactivity from the heart were very similar between [^{99m}Tc]MAMA-HDA and [^{125}I]-IPPA. In sum, ^{99m}Tc -labeled MAMA medium-chain fatty acid analogue is peculiarly propitious for hepatobiliary imaging, while ^{99m}Tc -labeled MAMA long-chain fatty acid analogue is optimal for myocardial imaging. Furthermore the tracers are metabolized via beta-oxidation in the heart and the liver.

^{99m}Tc -CpTT-fatty Acid Analogues

A series of radiotracers, ^{99m}Tc -CpTT-fatty acid analogues (Figure 1b), were prepared in high radiochemical yield ($\sim 63\%$ decay-corrected) by a double ligand transfer reaction between the ferrocene adduct of fatty acid methyl ester and $\text{Na}^{99m}\text{TcO}_4$ in the presence of $\text{Cr}(\text{CO})_6$ and CrCl_3 , followed by hydrolysis of the methyl ester group. Those radiotracers were shown to be chemically stable when incubated in serum. 8-Cyclopentadienyltricarbonyl technetium-99m 8-oxooctanoic acid (^{99m}Tc -CpTTOA) [25] was metabolized to 4-cyclopentadienyl tricarbonyl technetium-99m 4-oxobutanoic acid (^{99m}Tc -CpTTBA) via beta-oxidation in the liver (Figure 1b), which supported that the beta-oxidation was the main metabolic pathway of this medium chain fatty acid analogue. Planar images of rats injected with ^{99m}Tc -CpTTOA showed accumulation of the radioactivity in the liver, kidneys, and bladder with rapid hepatic clearance as a function of time. On the basis of these findings, ^{99m}Tc -CpTT-PA [19] and ^{99m}Tc -CpTT-16-oxo-HDA [20] were prepared as long chain fatty acid analogues for energy production in the myocardium (Figure 1b). Biodistribution of ^{99m}Tc -CpTT-PA and ^{99m}Tc -CpTT-16-oxo-HDA in rats or mice showed high radioactivity accumulation in heart with rapid clearance and high heart to blood uptake ratios, and the tracers were metabolized to ^{99m}Tc -CpTT-propionic acid and ^{99m}Tc -CpTT-4-oxo-butyric acid via beta-oxidation in myocardium, respectively. [^{99m}Tc]CpTT-PA was similar to [^{125}I]-IPPA with radioactivity uptakes in the heart after 1 min pi. ^{99m}Tc -CpTT-PA showed a slow blood clearance at earlier pi time, whereas a gradual increase in radioactivity in the blood was observed with [^{125}I]-IPPA from 2 to 30 min pi. In contrast, the radioactivity levels in the liver remained unchanged after injection of [^{125}I]-IPPA, whereas ^{99m}Tc -CpTT-PA showed a gradual increase with times. In addition, 15-Cyclopentadienyl tricarbonyl technetium-99m 15-oxo-pentadecanoyl thiopheneacetic acid (^{99m}Tc -CpTT-15-oxo-PTA) [26] was synthesized using alkyl group inserted in the beta-position of the chain to interfere with metabolism of the tracer. After intravenous administration of ^{99m}Tc -CpTT-15-oxo-PTA, the tracer showed highest uptake of $9.39 \pm 1.10\%$ ID/g at 1 minute and followed by moderate clearance from the rat heart. The maximum heart to blood ratio of

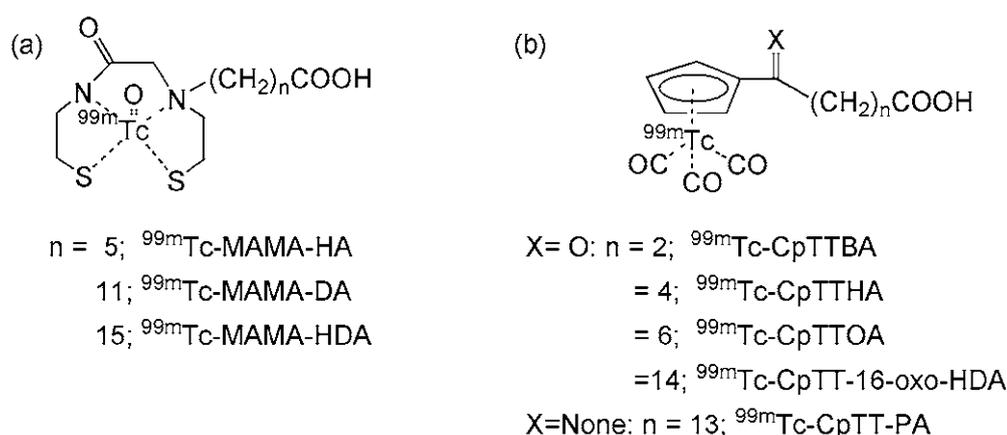
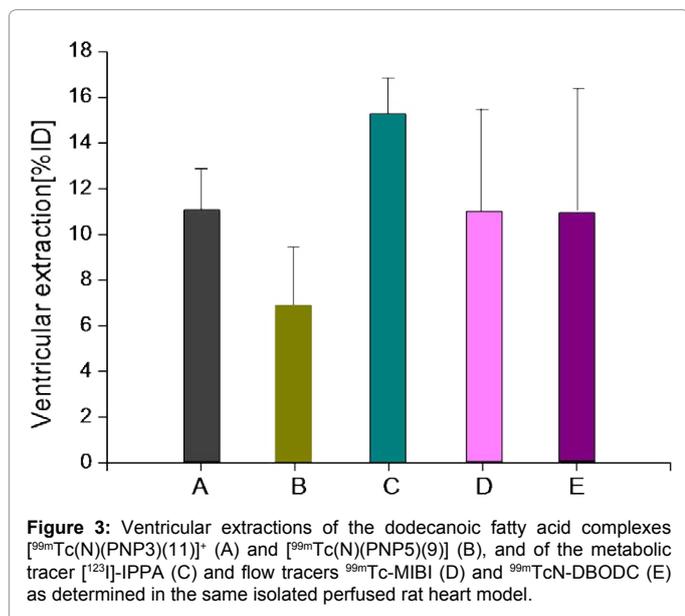
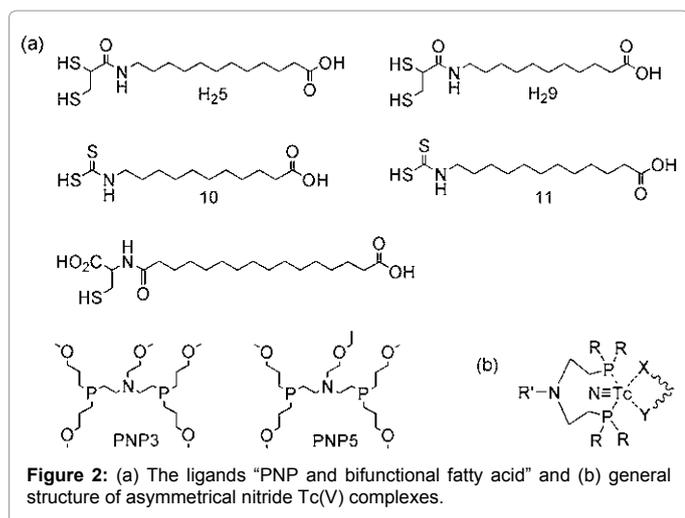


Figure 1: General structure for (a) ^{99m}Tc -MAMA-fatty acids and (b) ^{99m}Tc -CpTT-fatty acids.

^{99m}Tc -CpTT-15-oxo-PTA (5.7 at 15 min pi) was higher than the tracers, ^{99m}Tc -CpTT-PA (4.60 at 10 min postinjection) and ^{99m}Tc -CpTT-16-oxo-HDA (3.76 at 30 min postinjection). Metabolite analysis showed ^{99m}Tc -CpTT-15-oxo-PTA was not metabolized via beta-oxidation in the heart. Thus, the metabolic mechanism is different from that of ^{99m}Tc -MAMA-HDA, ^{99m}Tc -CpTT-PA and ^{99m}Tc -CpTT-16-oxo-HDA.

$^{99m}\text{Tc}(\text{N})(\text{PNP})^{2+}$ fatty Acid Analogues (PNP=Diphosphane Ligand)

The ^{99m}Tc -labeled fatty acid analogues, $^{99m}\text{Tc}(\text{N})(\text{PNP})(\text{L})^{0/+}$ (PNP = diphosphane ligand; L = dianionic or monoanionic bifunctional fatty acid analogues) (Figure 2), exhibit the asymmetrical structure with a $\text{Tc}\equiv\text{N}$ group surrounded by a tridentate (PNP) and a bidentate (L) chelating fatty acid analogues [27]. The fragment $^{99m}\text{Tc}(\text{N})(\text{PNP})^{2+}$ provides a electrophilic metal moiety for the attachment of the site-specific group, which were functionalized by appending a bis-mercapto or a dithiocarbamate π -donor chelating systems to one terminus of the fatty acid analogues. The experiments in rats showed that the ^{99m}Tc -labeled monocationic fatty acid $^{99m}\text{Tc}(\text{N})(\text{PNP3})(11)^+$ (Figure 2) were the same as the monocationic tracers, ^{99m}Tc -MIBI and ^{99m}Tc -DBODC, with almost identical accumulation in myocardium (Figure

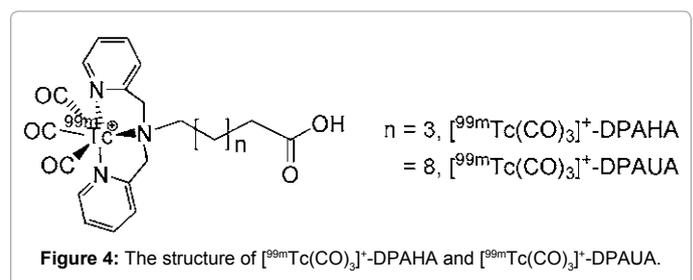


3). Conversely, the ^{99m}Tc -labeled fatty acid neutral complexes were not efficiently accumulated in heart and rapidly washed out. It indicates that the fatty acid analogue with the monopositive charge is more beneficial to myocardial uptake than neutral complexes. Comparison of the observed kinetic behavior of the ^{99m}Tc -labeled fatty acid neutral complexes in the isolated perfused rat heart model with that of the myocardial metabolic tracer ^{123}I -IPPA revealed that the introduction of the metallic moiety partially hampers recognition of the ^{99m}Tc -labeled fatty acids by cardiac enzymes (Figure 3), and consequently, their behavior did not completely reflect myocardial metabolism.

Our group previously synthesized the ^{99m}Tc -labeled monocationic fatty acids, $^{99m}\text{Tc}(\text{CO})_3^+-\text{DPAHA}$ and $^{99m}\text{Tc}(\text{CO})_3^+-\text{DPAUA}$ (Figure 4), which showed higher initial myocardial uptake in normal mice, followed by slow clearance [28,29]. By estimating the animal experiments and the theoretical calculations of the molar volume and the solvation free energy of technetium-99m chelating groups, a small-size and monocationic technetium-99m core is beneficial to enhance the myocardial accumulation with high heart-to-blood uptake ratios (such as $^{99m}\text{Tc}(\text{N})(\text{PNP3})(\text{L})^+$) and reduce radioactivity accumulation in liver for the ^{99m}Tc -labeled fatty acids. From the higher initial myocardial uptake and slow clearance, the kinetic behavior of the monocationic complexes was much closer to that of the fatty acid analogues $^{99m}\text{Tc}(\text{N})(\text{PNP3})(11)^+$ than the myocardial metabolic tracer ^{123}I -IPPA. Another ^{99m}Tc -labeled hexadecanoic acid with $^{99m}\text{Tc}(\text{N})(\text{PNP})^{2+}$ core resulting in a neutral complex [1] was reported that the asymmetric [2+2] complex cleared faster from the non-target organs, namely, liver, lungs, and blood compared to that of ^{123}I -IPPA. However, the compounds exhibited lower uptake and faster washout from the myocardium as compared to ^{123}I -IPPA, which might have demonstrated again that the ^{99m}Tc -labeled fatty acid analogues with one monopositive charge are more advantageous to myocardial uptake and retention than the neutral ones, and their behaviors still did not completely reflect myocardial metabolism.

“4 + 1” Mixed Ligand Technetium-99m-labeled Fatty Acid Analogues

Technetium-labeled fatty acids for myocardial metabolism imaging were synthesized according to the “4 + 1” mixed-ligand approach, where the metal core in the oxidation states +3, well-wrapped in a trigonal-bipyramidal coordination moiety, is attached at the ω -position of a fatty acid chain. Walther groups reported a series of “4 + 1” mixed ligand ^{99m}Tc -labeled fatty acids (Figure 5a), which the technetium-99m is coordinated by both a tetradentate NS3 chelator and a monodentate isocyano fatty acid coligand with different chain length [30]. The tracers all showed high ventricular extraction rates in isolated perfused rat hearts (up to 26 %ID), which exceed considerably that of the iodinated fatty acid ^{123}I -IPPA (15.51 %ID). In particular, the tracer C11S [29] had a noticeable heart uptake of 2% ID/g at 5 min pi and a good heart to blood ratio of 8.6 at 5 min pi in biodistribution studies, which is superior to other described ^{99m}Tc -fatty acid mimics. The heart to liver ratio of 0.25 at 5 min pi was improved, which indicated that the



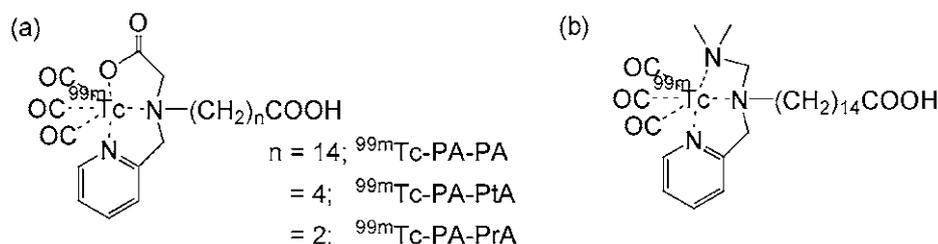


Figure 6: General structure for tricarbonyl ^{99m}Tc -labeled fatty acids.

scar [36,37]. In addition, absence of uptake of BMIPP in a minority of patients without any significant cardiac abnormality raised the question of the mechanism of fatty acid transport into the cells [38]. Therefore the easy availability radionuclide Tc-99m acted as a surrogate to the iodide has been used to develop Tc-99m chelating fatty acid tracers, but so far the work are not quite smooth.

Technetium-labeled fatty acid analogues have been developed by introducing Tc-99m chelate to the terminal position of straight-chain fatty acid. Among all the ^{99m}Tc -labeled fatty acids, the half-life of aerobic beta-oxidation of these fatty acids is fast and in the order of minutes. The remainder of the total tracers incorporating into the lipid pool, mainly in the form of triglycerides and phospholipids, presents in the myocardium or liver for a long time. Turnover in the lipid pool is very slower, with a half-life of hours [4]. In addition, the introduction of metal chelate disturbs the inherent nature of the fatty acid, which alters the molecular structure and hydrophobicity compared with the natural compound. To overcome the problems including Tc-99m chelate resulting in a low uptake in myocardium or hepatocyte and linear alkyl chain based on beta-oxidation leading to a rapid clearance from tissues, technetium-labeled fatty acids are developed by varying the chelating ligand and branching alkyl chain of fatty acid (Figure 1). The common method prolonging myocardial/hepatic retention is metabolic trapping by inhibition of beta-oxidation through the introduction of methyl branching (or sulfur atoms) at the beta-carbon position. A Tc-99m core with high stability and relative small molecular size is very useful to abate the negative influences on the structure of fatty acids and enhances target organ uptakes of fatty acid analogues.

Recently, a variety of Tc-99m cores have been used for fatty acid tracers, such as $\text{fac-}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$, $\text{fac-}^{99m}\text{Tc}(\text{O})\text{MAMA}$, $\text{fac-}^{99m}\text{Tc}(\text{N})(\text{PNP})^{2+}$, and so on, which are the very versatile moieties to react with various chelating fatty acids under their corresponding conditions. The " $\text{fac-}^{99m}\text{Tc}(\text{CO})_3^+$ " chelate with the stability, significantly smaller size and easy synthesis offers exciting possibilities for fatty acid labeling [24]. Particularly, the diminutive and lipophilic cyclopentadienyl tricarbonyl Tc-99m core ($^{99m}\text{Tc-CpTT}$) only minimally perturbs biological activity of fatty acid. In the chelating groups of $^{99m}\text{Tc-CpTT-PA}$ and $^{99m}\text{Tc-CpTT-16-oxo-HDA}$, ω -cyclopentadienyl fatty acids chelated the $\text{fac-}^{99m}\text{Tc}(\text{CO})_3^+$ complex, which showed the tracers had high chemical stability in vitro and high initial radioactivity accumulation but with rapid myocardial washout and higher blood background than that of ^{125}I IPPA. However, the fatty acid tracers with other Tc-99m cores, such as $^{99m}\text{Tc-MAMA-HA}$, $^{99m}\text{Tc}(\text{N})(\text{PNP3})(11)^+$, $^{99m}\text{Tc}(\text{N})(\text{PNP5})(9)$, $^{99m}\text{Tc}(\text{CO})_3^+-\text{DPAUA}$, and so on, demonstrate lower uptake and target to nontarget ratio than ^{125}I -IPPA and bring other new disadvantages to fatty acid itself at the same time. Consequently, smaller size Tc-99m core for fatty acid is indispensable to overcome the perturbation and enhance uptake, and the insertion of blocking group for inhibition of β -oxidation may prolong myocardial/hepatic retention of fatty acid. Unfortunately,

a series of branching alkyl chain of "4 + 1" mixed-ligand technetium labeled fatty acids [30] has not been found in which both properties are combined properly. Thus, both diminutive Tc-99m core and blocking group are essential to improve the SPECT imaging quality with high uptakes and long retention of fatty acids.

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