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Imaging of Myocardial Fatty Acid Oxidation

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Abstract

Myocardial fuel selection is a key feature of the health and function of the heart, with clear links between myocardial function and fuel selection and important impacts of fuel selection on ischemia tolerance. Radiopharmaceuticals provide uniquely valuable tools for in vivo, non-invasive assessment of these aspects of cardiac function and metabolism. Here we review the landscape of imaging probes developed to provide noninvasive assessment of myocardial fatty acid oxidation (MFAO). Also, we review the state of current knowledge that myocardial fatty acid imaging has helped establish of static and dynamic fuel selection that characterizes cardiac and cardiometabolic disease and the interplay between fuel selection and various aspects of cardiac function.

Introduction

Significance of MFAO in health and disease

Although the heart is a metabolic omnivore, fatty acids are the dominant myocardial fuel under usual circumstances in health and disease [1]. The balance between fuel types can be shifted as an externally imposed change that affects myocardial fuel selection, or as intrinsic changes that are the result of myocardial disease.

Primary sites of regulation of fuel selection and MFAO include transmembrane transport, oxidative and non-oxidative fatty acid metabolic processes, levels of regulatory intermediates, and external regulators like insulin or catecholamines. The importance of these sites as targets of regulation or sites of disease-related imbalance is beginning to be explored.

Fuel selection impacts oxidative efficiency, i.e. efficiency of energy generation per unit O_2 used. This also impacts work efficiency (work produced per unit O_2 used) but the importance of shifts in oxidative efficiency on MFAO, contractile function or other outcomes of importance has not yet been well explored.

Significance of MFAO imaging

Measurement of fuel selection in the heart is challenging. Ex vivo experiments on isolated hearts are extremely useful but incompletely informative, and ultimately measurements in vivo in circumstances of health and disease are needed. The traditional methods of ‘organ balance’ measurements of fuel metabolism require measurements of rates and amounts of

fuel delivery and uptake, using invasive tools to make samples and measurements of analyte blood concentrations. Imaging tools provide a major advantage in animal and human studies, because a set of in vivo measurements can be made with only modest needs for blood sampling to assess metabolite concentrations. Particularly for evaluations of myocardial metabolism, tracer-based methods have been advanced that provide arterial measurements of imaging tracers, obviating the need for peripheral arterial sampling. Together with progressive advances in the design and production of radiolabeled fatty acid probes, and in the modeling approaches to extracting relevant kinetic parameters from the time-activity curves, imaging studies can provide accessible, accurate and quantitative measurements of MFAO safely and noninvasively. These tools have already provided major advances in our understanding of myocardial fatty acid metabolism, and of fuel metabolism more generally, in health and disease. In the following sections we will review the state of the art in radiopharmaceutical tracers that allow non-invasive measurement of MFAO, followed by a review of the knowledge that these approaches have provided for us in realms of human health and disease.

Radiopharmaceuticals for MFAO Imaging

Metabolically Cleared MFAO Probes

The central role of fatty acids in energy provision to the myocardium motivated efforts to develop radiolabeled long-chain fatty acids (LCFAs) that could be imaged by PET or SPECT. As early as 1976, the synthesis of 1-^{11}C-palmitate (CPA, $T_{1/2}$ = 20 min, Figure 1) had been achieved and this radiotracer was evaluated in isolated perfused rabbit hearts and in living dogs[2]. CPA has been used extensively in cardiovascular PET research studies to monitor changes in palmitate uptake and metabolism in response to physiologic conditions and pathologies ([3–6]). Compartmental modeling of myocardial time-activity curves allows estimation of CPA uptake, esterification and oxidation [7]. However, the modeling technique has not been validated in conditions of myocardial ischemia, where enhanced backdiffusion of unoxidized CPA is confounded with metabolic clearance of β-oxidized CPA. The utility of CPA for indication of MFAO is therefore limited to conditions that exclude myocardial ischemia. Fluorine-18 labeled LCFA analogs were developed to take advantage of the longer isotopic half-life of ^{18}F ($T_{1/2}$ = 109.8 min) for radiotracer distribution and more practical clinical PET imaging logistics [8]. In mice, the odd-chain length LCFA analog, 17-^{18}F-fluoroheptadecanoic acid (FHA, Figure 1) was found to have rapid uptake in heart similar to CPA with biphasic clearance from the myocardium. The even-chain LCFA analog, 16-^{18}F-fluorohexadecanoic acid (FHDA, Figure 1) also showed similar biphasic clearance from the heart, but with different clearance rates, and different labeled metabolites in the heart as predicted by their different end-products of β-oxidation. Bone uptake was highest for FHA, consistent with end-stage metabolic defluorination of the putative radiolabeled metabolite, 3-^{18}F-fluoropropionyl-CoA. In the case of FHDA, the primary putative metabolite is 2-^{18}F-fluoroacetyl-CoA, which may undergo a variety of metabolic transformations, including defluorination. The complex metabolic handling of the ^{18}F-labeled LCFA analogs, in addition to their *in vivo* defluorination, complicates the development of quantitative modeling strategies. To provide a more metabolically stable ^{18}F-labeled LCFA analog, Tu et al. [9] recently synthesized 15-(4-(2-^{18}F-fluoroethoxy)phenyl)pentadecanoic acid (F7,

Figure 1) that showed dramatically reduced *in vivo* defluorination. F7 showed robust uptake in rat myocardium and a biphasic clearance pattern. Quantitative data analysis for estimation of myocardial fatty acid metabolic fluxes has yet to be shown with F7.

The radioiodinated LCFA analog, ^{123}I-iodophenylpentadecanoic acid (IPPA, Figure 1), was developed for SPECT imaging applications [10]. In myocytes, radioiodinated IPPA is esterified to form labeled complex lipids and metabolized by β-oxidation to the predominant metabolite, iodobenzoic acid and other short chain oxidation end-products [11, 12]. In a canine model of regional low-flow ischemia, initial uptake of IPPA was lower in ischemic regions relative to non-ischemic regions, however myocardial clearance rate was significantly slower in ischemic regions leading to relatively increased retention of radioactivity in ischemic myocardium at later intervals [13]. The longer acquisition periods required for SPECT imaging limits the utility of IPPA for determining clearance kinetics from the human myocardium. Compartmental modeling was applied to the kinetics of IPPA in isolated rat heart [14], but application of modeling strategies in humans has been limited by the complex metabolic fate of the tracer.

Metabolically Trapped MFAO Probes

To simplify the myocardial kinetics of radiolabel LCFAs, structural modifications were investigated to impede oxidation or esterification. The 3-methyl branched chain analog, β-methyl-1-^{11}C-heptadecanoic acid (β-Me-HA, Figure 1) was developed to inhibit β-oxidation [15]. In PET imaging studies, β-Me-HA showed prolonged retention in normal and infarcted dog myocardium. Quantitative autoradiographic imaging of rats administered β-methyl-1-^{14}C-heptadecanoic acid showed the highest heart concentration at 60 min post-injection, with myocardial concentration diminishing to 0.4% injected dose/g at 24 h [16]. Terminally ^{18}F-labeled branched chain LCFA analogs have also been pursued. 3-Methyl-17-^{18}F-fluoroheptadecanoic acid (3MFHA, Figure 1) and 5-methyl-17-^{18}F-fluoroheptadecanoic acid (5MFHA, Figure 1) showed somewhat lower initial uptake than unbranched FHDA in rat heart [17]. Clearance rate from the heart was slowest for 3MFHA, while clearance of 5FMHA was similar to the unbranched analog FHDA. Metabolic defluorination was evident for both 3MFHA and 5MFHA. Further work is required to understand the differences in metabolic handling of 3MFHA and 5MFHA and the potential for quantitative modeling of their myocardial kinetics using PET. For SPECT imaging, the ^{123}I-labeled β-methyl substituted probe β-methyl-15-^{123}I-iodophenylpentadecanoic acid (β-MeIPPA, Figure 1) has been used extensively in animals and humans [18–21]. Metabolic studies have elucidated that BMIPP is a substrate for α-oxidation followed by β-oxidation in the myocardium [22–24]. However, since BMIPP is not accepted for mitochondrial transport by the CPT-1 dependent shuttle system [25], its early retention in myocardium reflects activation and esterification to complex lipids with slow turnover related to α-oxidation rate. Its utility as an MFAO probe is therefore very limited.

LCFA imaging probes modified by heteroatom substitution with stable or radioactive tellurium isotopes were investigated by Knapp and colleagues [26–28]. The LCFA analog 9-^{123m}Te-telluraheptadecanoic acid (9-TeHA, Figure 1) was shown to have prolonged retention in rat and dog myocardium [26]. Although the metabolism of these analogs was

not fully elucidated, their slow myocardial clearance was presumed to reflect incomplete β-oxidation caused by the tellurium heteroatom. Heteroatom substitution with sulfur was subsequently pursued by DeGrado and colleagues as a more physiologically acceptable substitution in LCFA probes [29]. Indeed, the 6-thia LCFA analog, 14-^{18}F-fluoro-6-thia-heptadecanoic acid (FTHA, Figure 1) was shown to exhibit >100 heart:blood concentration ratio with prolonged myocardial retention. ^{18}F-labeling at the ω-3 position was developed to minimize in vivo defluorination in rodent models, but subsequent studies in pigs [30] and humans [31] showed that terminally ^{18}F-labeled thia fatty acids do not exhibit appreciable metabolic defluorination in these higher mammals. Inhibition of MFAO with a CPT-1 inhibitor caused an 81% reduction in murine heart uptake of FTHA, indicating specificity of uptake for imaging of MFAO [29]. Indeed, very low incorporation of ^{18}F into complex lipids showed FTHA to have a low esterification rate. The ^{18}F-radiolabel was found to bind to mitochondrial protein in the myocardium, presumably through a long-chain thiol β-oxidative metabolite [29]. PET studies in healthy human volunteers showed the myocardial trapping rate of FTHA to be increased with exercise but unchanged with elevated blood flow induced by dipyridamole [32]. However, a later study with FTHA in hypoxic canine myocardium showed retention in hypoxic myocardium independent of β-oxidation rate [33]. It was subsequently shown that sulfur substitution at the 4th carbon enhanced specificity of thia fatty acid analog probes for indication of MFAO [30]. Myocardial uptake of the palmitate analog, 16-^{18}F-fluoro-4-thia-hexadecanoic acid (FTP, Figure 1), was shown to track β-oxidation rates in normal and hypoxic perfused rat heart [30]. Further quantitative validation studies for FTP were performed in isolated perfused rat heart to define the relationship of MFAO (measured using tritiated palmitate) to FTP trapping rate in myocardium under diverse conditions [34]. The concept of a “lumped constant” (LC) for FTP was invoked, as analogous to the lumped constant utilized for quantitation of glucose phosphorylation using ^{18}F-FDG. Recently, DeGrado et al. [35, 36] have described an oleate analog of (FTO, Figure 1) which shows high specificity for MFAO imaging and enhanced myocardial retention relative to FTP in rat myocardium. Since oleate is the most prevalent LCFA in the blood, and is highly utilized as an energy-providing fatty acid [37], the oleate imaging analog, FTO, may provide higher sensitivity and specificity for MFAO imaging than palmitate analogs [36].

Incorporation of a cyclopropyl group is another structural modification employed to inhibit oxidation of LCFA imaging probes in heart. Shoup et al. [38] have developed trans-9(*RS*)-^{18}F-fluoro-3,4(*RS,RS*)-methyleneheptadecanoic acid (^{18}F-FCPHA, Figure 1) with the cyclopropyl group encompassing carbons 3 and 4. ^{18}F-FCPHA showed high uptake and prolonged retention in rat heart. The metabolism of ^{18}F-FCPHA and its specificity for imaging of MFAO have yet to be clarified.

MFAO imaging in ischemic heart disease

The application of fatty acid oxidation imaging to myocardial ischemia has been in two overall areas of interest. First is the pathophysiologic question of the shifts in fuel selection in ischemic myocardium. Second is the more clinically approachable application of using fatty acid imaging to identify and quantify regions of ischemia. We will further explore each of these topics.

The heart does not maintain a significant depot of stored fuel substrate, and in the absence of ongoing supply of fuel and oxygen myocardial cells are able to sustain metabolism for only a duration of minutes. In the region of the myocardium subjected to ischemia, impaired fuel availability and hypoxia necessarily produce local shifts in fuel selection. These shifts, and accompanying changes in blood flow rates and distribution, have been studied in part using tracer-based methodologies, including SPECT and PET imaging [39–44]. Most such studies have used radiolabeled glucose (to quantify glucose uptake) and radiolabeled acetate (to quantify blood flow or perfusion), without concurrent imaging of fatty acid kinetics. Fuel selection is reciprocal between glucose and fatty acids, and the studies that have used fatty acid tracers overall have provided complementary findings compared to those measuring glucose. Specifically, ischemic myocardium metabolizes glucose preferentially, with reduced MFAO [45–47], with some sensitivity of the magnitude of the observed response to the specific fatty acid tracers used [47]. Post-ischemic changes in metabolism in the affected zone have also been described [48], with recovery of fatty acid metabolism directly associated with recovery of perfusion. Some studies of anti-ischemia approaches have used fatty acid imaging to evaluate effectiveness of treatment as well as the specific effects on myocardial fuel selection [40, 49]. These observations demonstrate the utility of fatty acid kinetic assessment using radionuclide imaging to elucidate the pathophysiology of ischemia, and increasingly to explore the mechanisms of benefit of novel anti-ischemic treatment approaches.

PET imaging in ischemia finds clinical utility in the estimation of infarct size, and more specifically in distinguishing viable from non-viable regions in the infarcted zone [34, 41, 42, 50–62]. PET measures of blood flow in ischemia can provide prognostic information [58, 63], and some have even argued that a PET-derived metabolic definition of infarct is superior to other imaging approaches [64]. Tracers of fatty acid uptake are similarly informative in these applications [65–70], and in some instances have been found to provide superior diagnostic and prognostic information [65, 67, 71] (Figure 2) and insights into the metabolic physiology underlying metabolic adaptation to ischemia and recovery in reperfused tissue [70, 72].

Despite the widespread clinical availability of PET methodology, particularly that using ^{18}F-fluorodeoxyglucose (FDG), to date PET has not found widespread application in clinical cardiology. Nevertheless, the value of PET-based measurements of glucose or fatty acid kinetics in providing non-invasive assessment of physiology has been clearly demonstrated, and tracers of fatty acid metabolism can provide unique information about the metabolic shifts accompanying various degrees and stages of ischemic injury.

MFAO imaging in heart failure

Myocardial fuel selection is abnormal in heart failure. Imaging of MFAO has contributed to our understanding of these phenomena, and their contribution to progression or recovery of disease. In parallel, fatty acid imaging has been applied in studies of treatments targeting cardiac dysfunction including those targeting myocardial metabolism directly. These therapeutic studies have also contributed to our understanding of the contributions of metabolic dysfunction to the pathogenesis of heart failure.

In heart failure, there is abnormal fuel metabolism overall, with variably reported shifts toward glucose with reduced fatty acid uptake, or away from glucose with increased fatty acid uptake. The majority of reports include increased fatty acid uptake, whether the underlying problem is ischemia [73], a non-ischemic cardiomyopathy [74–77], or a diabetic cardiomyopathy [78, 79], but others report reduced fatty acid uptake in idiopathic cardiomyopathy [80]. It is unclear whether these various conditions produce altered fatty acid utilization via the same mechanisms, how increased fatty acid transport relates to the impairment of function, and what the developmental time course of metabolic and mechanical dysfunction, and the inter-relationships of these changes, might be. Specifically, it is possible that changes in fuel selection result directly from compensatory changes due to impaired function (which may be a shared phenomenon driving metabolic shifts across various etiologies of dysfunction). It is also possible that the metabolic changes are in response to the whole-body response to impaired cardiac function or tissue perfusion (mediated for example by myokines, cytokines, or neurologically-driven changes). Mechanisms for these potential effects have not been systematically investigated. It is known that in health the myocardium responds to acute *increases* in fat exposure with an acute reduction in mechanical function [81], but conversely acute *reduction* in myocardial fat in cardiomyopathy is also associated with impaired function [82]. An increase in fatty acid uptake directly in response to impairment of mechanical function has not been demonstrated with imaging methods, but such changes are seen with experimentally imposed pressure overload [83, 84]. The underlying abnormalities include alterations in regulatory metabolic intermediates such as malonyl-CoA, and adverse changes in mitochondrial content and function [85–87].

There have been a small number of studies using fatty acid imaging as a measurement endpoint in clinical studies of heart failure, in particular in studies of metabolic modulators targeting abnormal fatty acid metabolism rates [77, 88–91]. Overall these show the anticipated restoration of fatty acid uptake and oxidation toward normal, in association with an improvement in function. These observations confirm that the metabolic and functional aberrations are strongly interconnected, and demonstrate that the metabolic abnormalities are not a fixed feature of the dysfunctional hearts.

An interesting and relatively recent observation made using myocardial fatty acid imaging studies is that there is a sex difference in the rates of myocardial fatty acid uptake, and oxidation with higher rates observed in women under normal physiologic conditions and with dysfunction [92–97]. These differences in turn relate to sex differences in metabolic efficiency in the heart and sex-related differences in the relationships among metabolism, efficiency, and mechanical function [92, 93, 98], and in responses to treatment [95]. This set of observations may provide novel insights into the longstanding unexplained sex difference in cardiac disease [99]. The molecular phenomena underlying these sex-specific changes in fuel selection, and the clinical implications of these recent observations, are only beginning to be explored.

MFAO imaging in obesity and diabetes

Abnormal fuel selection is a feature of skeletal muscle in obesity in type 2 diabetes [100], generally in the setting of resistance to the actions of insulin to drive glucose uptake and utilization (i.e. tissue insulin resistance). Parallel phenomena are at play in the heart, where there is now evidence that abnormally increased uptake of fatty acids, beyond the baseline preference for fatty acid, contributes to metabolic abnormalities in the heart in obesity and diabetes [78, 98, 100–112] (Figure 3). Many of these observations have been uniquely made possible by the availability of non-invasive quantitative assessments of fuel flux using radiolabeled glucose [95, 103, 113–116] and fatty acid tracers [78, 92, 95, 98, 103, 105, 109, 114, 117–121], showing augmented fatty acid uptake and utilization under fasting conditions, and importantly impaired capacity to switch among fuel sources (i.e. metabolic inflexibility)[31, 105, 113, 115, 122] (Figure 4).

Although Type 1 diabetes (an insulin sensitive, insulin deficient state) and Type 2 diabetes (an insulin resistant, hyperinsulinemic state) are pathophysiologically distinct and produce different clinical heart disease risk patterns, they are both typified by abnormal increases in myocardial fatty acid uptake [104, 110, 113, 123]. This likely relates to the shared underlying myocardial preference for fatty acids, and the shared phenomenon of abnormal control of adipose lipolysis resulting in augmented fatty acid availability.

Interestingly, in the intermediate insulin resistant state of impaired glucose tolerance abnormally increased fatty acid uptake has been less consistently seen [100, 117, 118, 124], raising the possibility that effects of elevated fatty acid delivery may be sensitive to the accompanying glycemic state. However, recent observations that in obesity weight loss-associated reductions in fatty acid availability are associated with reductions in myocardial fatty acid uptake and improvements in cardiac function [117, 125] argue in favor of an adverse effect of augmented myocardial fatty acid uptake even in the non-diabetic state.

Imaging evaluation of myocardial fatty acid and glucose kinetics have been used to explore the effects of metabolically targeted therapies that alter systemic fatty acid metabolism, alter myocardial fatty acid uptake, or alter the metabolic fate of fatty acids [77, 104, 105, 113, 115, 126–128]. These disparate approaches have converged on a unified and convincing set of observations causally linking increased fatty acid delivery, uptake and MFAO to metabolic dysfunction in the heart.

The factors that drive diabetes and obesity-associated increases in myocardial fatty acid uptake and utilization, and the impaired capacity to switch among fuel sources remain incompletely understood. Also requiring further exploration are the mechanistic connection between abnormalities of fuel selection and abnormalities of myocardial function, and the previously mentioned sex differences in myocardial fatty acid utilization. Further studies applying myocardial fatty acid imaging will be needed to explore and better understand these phenomena.

Conclusions

Quantitiative imaging of myocardial fatty acid uptake and oxidation provides a uniquely valuable set of tools for clinical and research applications. The optimal fatty acid probe has not yet been defined, and work is ongoing attempting to optimize these probes by designing probes with specific metabolic fates or mitochondrial targeting, for example. The application of the probes available to date has defined abnormalities in myocardial fuel selection as a key feature of many cardiac and cardiometabolic diseases, with a small set of studies demonstrating that metabolically targeted therapies can produce improvements in myocardial function or ischemia tolerance. Future possibilities include more widespread application of MFAO imaging as a measure of cardiac injury with ischemia, with improved prognostic capabilities, and application as a research tool to explore in more detail the mechanisms and treatments of myocardial disease in obesity and diabetes.

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Highlights

- Myocardial fatty acid oxidation (MFAO) imaging allows in vivo assessment of cardiac fuel utilization.
- Fatty acid tracers and analysis models have been developed that allow detailed assessments of fuel kinetics in the heart.
- MFAO imaging has identified abnormalities of fuel selection in cardiac disease, and in cardiometabolic disease.
- MFAO imaging can be used clinically to identify regions of ischemia, and can be used in clinical trials to follow effects of therapies.

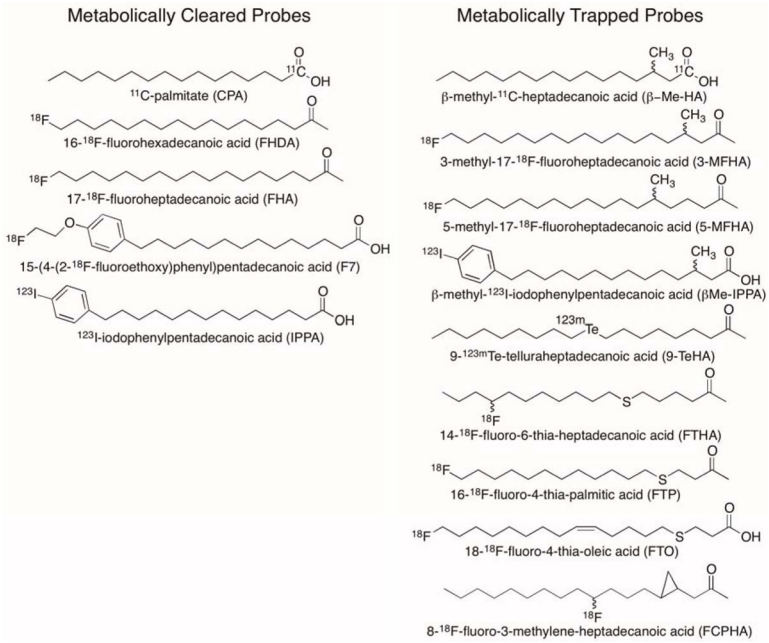

Figure 1.
Long-chain fatty acid metabolic probes.

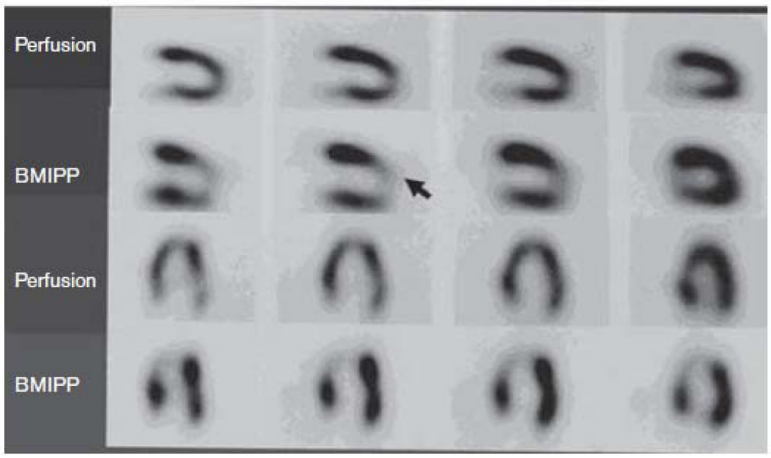

Figure 2.

SPECT imaging evaluating viable myocardium using a perfusion probe (99Tc-Tetrofosmin) and an MFAO probe (BMIPP). The arrow indicates the location of a severe stenosis of the left anterior descending coronary artery. Perfusion imaging was performed at the time of hospital admission, and BMIPP imaging was performed the following day. The authors conclude that the fatty acid uptake probe provides superior sensitivity for detecting the injured zone, and suggested that the metabolic probe could be used to assess a metabolic memory of the injury. From [122]

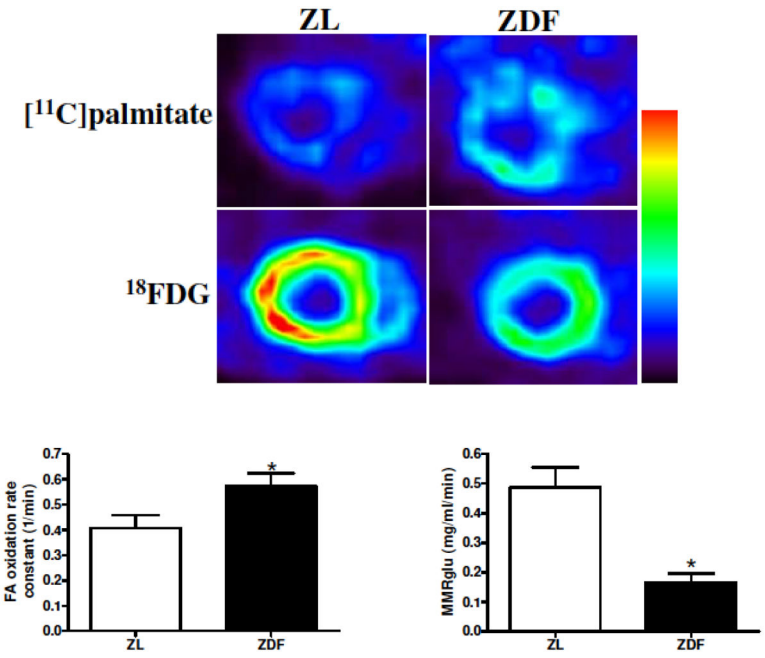

Figure 3.

Increased fatty acid uptake and oxidation, and lower glucose uptake, in obese fat-fed Zucker rats (ZDF) compared to age-matched lean Zucker rats (ZL). Upper panel, color-scale matched short-axis images of the myocardium demonstrating qualitatively increased fatty acid uptake and reduced glucose uptake in obesity. Lower panel, kinetic quantification of data from the time-activity curves. From [79]

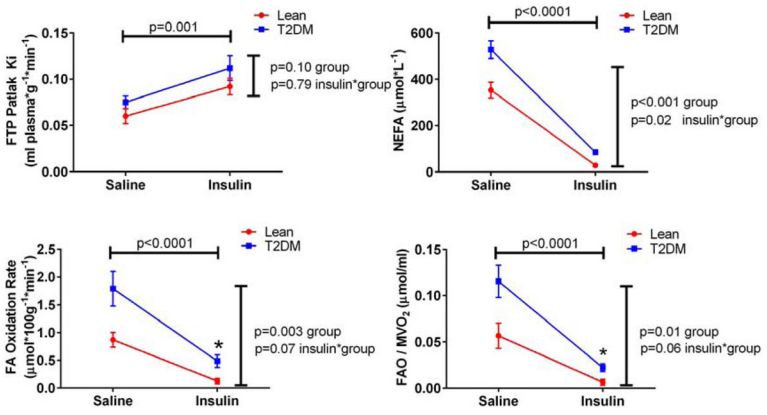

Figure 4.

Augmented fatty acid uptake and oxidation, reduced metabolic efficiency, and impaired insulin-induced fuel switching, in human Type 2 diabetes compared to age-matched lean controls. Fatty acid kinetics were measured using FTP, 18-^{18}F-fluoro-4-thia-oleic acid. NEFA, circulating non-esterified fatty acid; FAO, fatty acid oxidation rate; MVO2, oxygen consumption rate (estimated from acetate kinetics assessed by PET). Insulin induced major shifts in all of these parameters; this effect of insulin was statistically different between the two groups only for the suppression of NEFA, but the steady state values achieved under insulin stimulation differed for both FAO and FAO/MVO2. From [31]