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VIEWPOINT

Metabolic toxicity of the heart: Insights from molecular imaging

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Abstract There is convincing evidence that alterations in myocardial substrate use play an important role in the normal and diseased heart. In this review, insights gained by using quantitative molecular imaging by positron emission tomography and magnetic resonance spectroscopy in the study of human myocardial metabolism will be discussed, and attention will be paid to the effects of nutrition, gender, aging, obesity, diabetes, cardiac hypertrophy, ischemia, and heart failure.

The heart is an omnivore organ, relying on metabolic flexibility, which is compromised by the occurrence of defects in coronary flow reserve, insulin-mediated glucose disposal, and metabolic-mechanical coupling. Obesity, diabetes, and ischemic cardiomyopathy appear as states of high uptake and oxidation of fatty acids, that compromise the ability to utilize glucose under stimulated conditions, and lead to misuse of energy and oxygen, disturbing mechanical efficiency. Idiopathic heart failure is a complex disease frequently coexisting with diabetes, insulin resistance and hypertension, in which the end stage of metabolic toxicity manifests as severe mitochondrial disturbance, inability to utilize fatty acids, and ATP depletion.

The current literature provides evidence that the primary events in the metabolic cascade outlined may originate in extra-cardiac organs, since fatty acid, glucose levels, and insulin action are mostly controlled by adipose tissue, skeletal muscle and liver, and that a broader vision of organ cross-talk may further our understanding of the primary and the adaptive events involved in metabolic heart toxicity.

Introduction

Molecular imaging is a discipline that combines molecular biology and *in vivo* imaging, enabling the visualization of molecular processes in living organisms. In this review the role of metabolic imaging in the understanding of specific cardiac disease processes will be discussed. The focus is circumscribed to imaging tools which can provide quantitative

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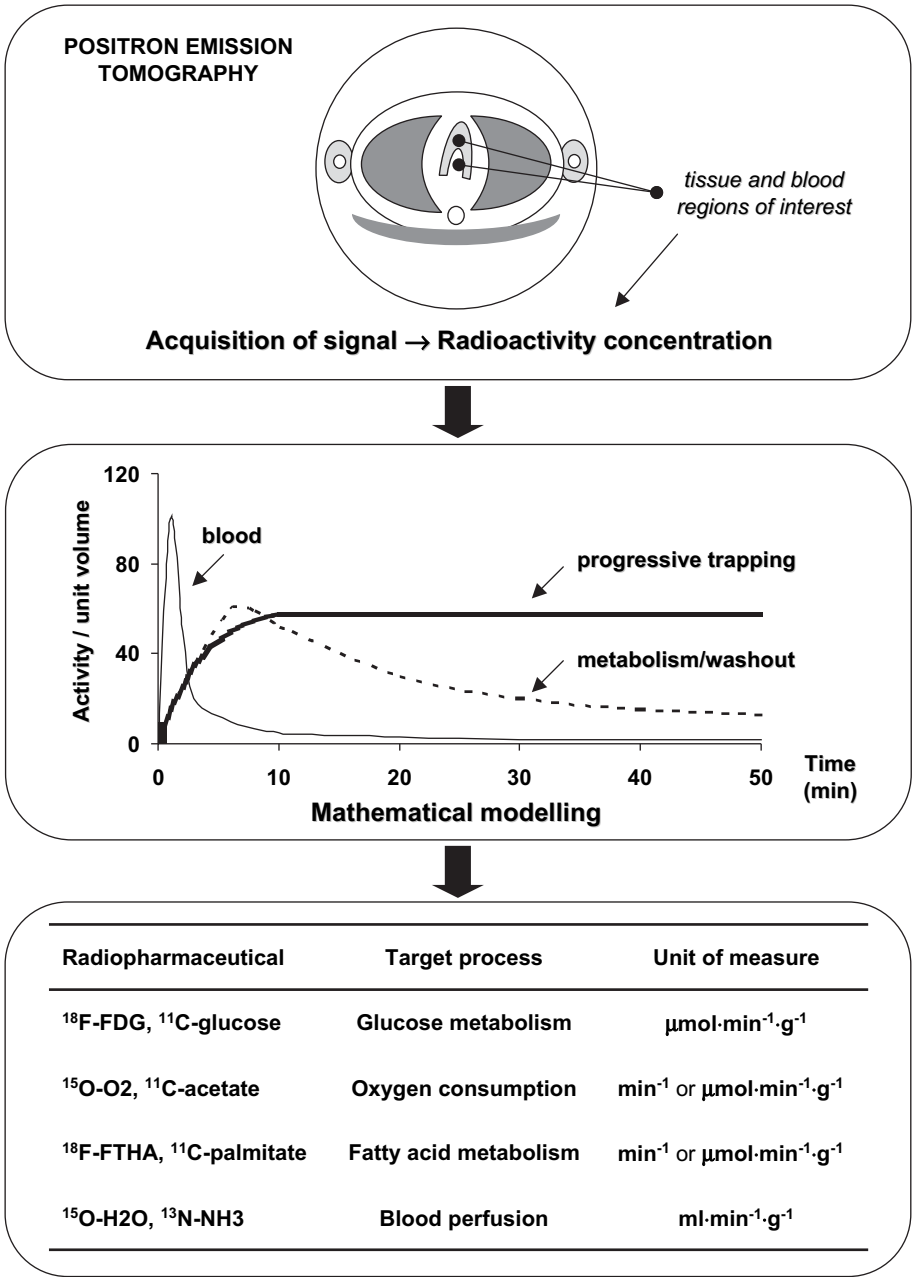
measurements of metabolic processes or substrate concentrations in the heart, namely Positron Emission Tomography (PET) and Magnetic Resonance Spectroscopy (MRS).

The former (Fig. 1) is primarily concerned with the assessment of organ perfusion, oxygen consumption, and glucose and fatty acid metabolism, by observation of the fate and kinetics of radioactively labelled substrates in the myocardium after intravenous administration. PET imaging is conducted under different experimental conditions, depending on the target process. Most common protocols



Radiopharmaceutical	Target process	Unit of measure
^{18}F-FDG, ^{11}C-glucose	Glucose metabolism	μmol·min^{-1}·g^{-1}
^{15}O-O2, ^{11}C-acetate	Oxygen consumption	min^{-1} or μmol·min^{-1}·g^{-1}
^{18}F-FTHA, ^{11}C-palmitate	Fatty acid metabolism	min^{-1} or μmol·min^{-1}·g^{-1}
^{15}O-H2O, ^{13}N-NH3	Blood perfusion	ml·min^{-1}·g^{-1}

Figure 1 PET is a nuclear imaging technique that employs short-lived positron-emitting radioisotopes to label molecules of interest (*e.g.*, substrate, perfusion indicator) and visualize their fate in individual organs. Emitted positrons annihilate when combined with an electron in the body tissue, generating two 511 KeV photons in quasi-opposite directions. Detectors are arranged all around the tissue of interest, and events interacting nearly simultaneously with opposite detectors are recorded and used to generate the image. After extracting from the image information pertaining to the time—activity concentration of tracer in the blood and cardiac wall, mathematical modeling is used to quantify the rates of metabolic processes within the target tissue. The main advantages of PET imaging are that it is functional and quantitative, the short-leaved nature of positron decay (<2 min to 110 min for the nuclides shown here) allows conduction of repeated studies, and most radionuclides (^{11}C, ^{13}N, ^{15}O) are isotopes of naturally occurring elements in the organic matter and can be substituted in the target molecule without altering its structure; others (^{18}F) are complexed to form analogues, which are meant to minimally or purposely affect the properties of the natural compounds. The most commonly used tracers and the corresponding target processes are shown in the bottom table.