Metabolic imaging in the metabolic syndrome

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Abstract

The metabolic syndrome is associated with a well known increased risk of coronary disease, but the syndrome or its components are also associated with adverse cardiac remodeling and decreased function [1,2]. Changes in myocardial substrate preference, efficiency, and energetics probably contribute to cardiac remodeling and dysfunction [3–5]. The focus of this review is on noninvasive imaging techniques and the insights they have provided on myocardial metabolism and the pathogenesis of noncoronary heart disease associated with the metabolic syndrome.
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Introduction

The healthy myocardium is an omnivore, able to use several different substrates for the production of ATP. Animal studies of obesity and insulin resistance, hallmarks of the metabolic syndrome, suggest that excessive myocardial fatty acid metabolism, whether oxidation, storage, or both, is directly detrimental to cardiac function [1,2]. There is little information evaluating the effect of the metabolic syndrome as a whole on human myocardial metabolism, but insights may come from evaluating how the different components of the metabolic syndrome affect myocardial metabolism.

The components of the metabolic syndrome are: abdominal obesity, triglyceride concentrations $\geq$ 150 mg/dL, high-density lipoprotein (HDL) concentration $<$ 40 mg/dL (men) or $<$ 50 mg/dL (women), blood pressure $\geq$ 130/85 mm Hg, or a fasting glucose concentration $\geq$ 110 mg/dL [3]. If a patient has any three of these, they have the metabolic syndrome, according to Adult Treatment Panel III guidelines. The metabolic syndrome is also associated with insulin resistance.

Imaging techniques for quantification of myocardial metabolism

Positron emission tomography

Positron emission tomography (PET) imaging in humans enables quantification of rates of myocardial substrate uptake and metabolism using radiolabeled tracers. Myocardial oxygen consumption (MVO_2) is quantified using carbon-11-labeled acetate; glucose uptake and utilization are quantified using fluorine-18-labeled fluorodeoxyglucose (FDG) or ^{11}C-glucose; fatty acid uptake, utilization, and oxidation are quantified either using compounds labeled with [^{11}F]-6-thia-heptadecanoic acid or using [^{11}C]palmitate; and lactate is quantified using [^{11}C]lactate. A PET scanner collects the gamma rays released after the collision of a positron (from a radiopharmaceutical) with an electron in tissue. *Figure 1* shows sample images from two [^{11}C]palmitate PET studies and the time–activity curves that are used in conjunction with compartmental modeling to quantify the myocardial uptake and utilization of fatty acid.

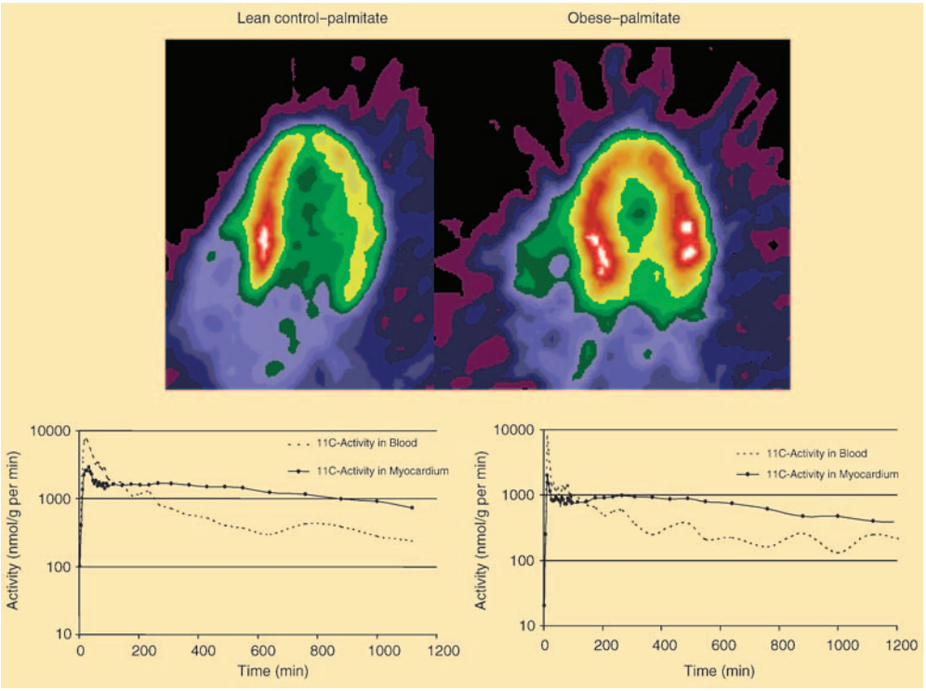

Figure 1. Top: Composite positron emission tomography (PET) myocardial images obtained from a young lean male (left) and a young obese female (right), 3–30 min after injection of [^{11}C]1-palmitate tracer. Images are displayed on the horizontal long axis with the base of the heart on top, septal wall on the left and lateral wall on the right. Compared with the lean control, the obese heart shows greater accumulation of tracer, indicative of greater uptake of free fatty acid (FFA). Bottom: Blood (···) and myocardial (–•–) time–activity curves obtained from the corresponding dynamic PET images of the same individual were used in conjunction with kinetic modeling to measure FFA uptake and oxidation (both in nmol/g per min). The obese individual had greater myocardial uptake, utilization, and oxidation of FFA than the lean control (eg, myocardial fatty acid utilization = 433 nmol/g per min compared with 87.6 nmol/g per min).

Limitations of PET include its high cost, and the need for a cyclotron to manufacture certain tracers. (Myocardial scintigraphy, another nuclear cardiology technique, is able to evaluate myocardial metabolism in a semiquantitative manner.)

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is similar to magnetic resonance imaging, in that both use the same type of scanner equipped with a large magnet to generate images. However, in addition to measuring the total signal emitted by the nuclei within the body and displaying an image, MRS allows for different chemicals or metabolites within a given volume of tissue to be tracked and displayed on a spectrum. For example, phosphorus-31 MRS is used to determine the relative amount of high-energy phosphates, eg, phosphocreatine (PCr) and adenosine triphosphate (ATP), within the heart. A low PCr : ATP ratio is generally believed to be deleterious, and is a predictor of cardiovascular mortality in patients with dilated cardiomyopathy [4]. Measurement of absolute concentrations of human cardiac high-energy phosphate is possible using 3-dimensionally resolved spectra [5].

Hydrogen-1 MRS may be used to quantify triglycerides deposited within the myocardium [6]. MRS-quantified triglyceride content correlates well with histochemical triglyceride quantification. Challenges in applying this approach to study of the metabolism of the human heart include accounting for the motion of the myocardium and contamination of the myocardial spectrum by pericardial fat. Because of the latter, the volume of interest is often placed in the interventricular septum.

Applying these imaging approaches to the metabolic syndrome

Myocardial metabolism in abdominal obesity and insulin resistance

In a study of young women, PET imaging demonstrated that body mass index (BMI) was linearly and positively correlated with MVO_2 and with the myocardial uptake, utilization, and oxidation of fatty acid [7]. Insulin resistance was even more closely related to fatty acid uptake and metabolism than was BMI [7]. Increased BMI also predicted decreased cardiac

efficiency [7]. Glucose utilization was not different between obese and nonobese individuals, although it was low in all (fasting) individuals. These data are consistent with studies in animal models of insulin resistance, which have demonstrated that increased myocardial fatty acid uptake and metabolism precede and contribute to decreased cardiac function [1,2,8]. The failure of other studies to demonstrate differences in myocardial fatty acid uptake and oxidation between those who were glucose intolerant and normal controls may relate to differences in tracers, numbers of individuals studied, sex, age, or baseline endogenous myocardial fat stores [9,10].

Accumulation of excess lipid in the myocardium may also be detrimental to the heart in obese individuals, via a process known as 'lipotoxicity' [1]. Supporting this, an [^{1}H]-MRS study showed that increased BMI was related to increased accumulation of triglyceride in human myocardium, and that this was related to impaired cardiac contractility [6,7].

Myocardial metabolism in diabetes mellitus

Fasting hyperglycemia, a component of the metabolic syndrome, is common to both type 1 and 2 diabetes mellitus. In a recent study, PET was used to demonstrate that individuals with type 1 diabetes mellitus had greater plasma free fatty acid concentrations, MVO_2, myocardial fatty acid utilization and oxidation, and lower glucose utilization, compared with nondiabetic controls [11]. A hyperinsulinemic/euglycemic clamp may increase glucose utilization in diabetic patients such that it is not different from controls [12,13]. This increased reliance on fatty acid metabolism at the expense of glucose metabolism by the myocardium is concordant with findings from animal studies and results in a loss of metabolic flexibility [14].

In type 2 diabetes mellitus, the data are more mixed. Some PET studies have demonstrated decreased myocardial glucose uptake, but others did not [15–17]. Nevertheless, rosiglitazone, an antidiabetic drug, has been shown to improve myocardial glucose uptake in patients with type 2 diabetes, with or without coronary artery disease [18,19].

A myocardial [^{31}P]-MRS study of patients with type 2 diabetes mellitus, however, clearly demonstrated that myocardial energy metabolism is abnormal, as diabetic patients (without overt cardiac disease) had impaired myocardial energy metabolism, manifested by a lower PCr : ATP ratio compared with controls. Moreover, myocardial PCr : ATP ratios correlated negatively with fasting plasma free fatty acid concentrations, suggesting a pathophysiologic link between excessive fatty acid availability to the heart and impaired energy metabolism [20].

Myocardial substrate metabolism in hypertension

In contrast to obesity and diabetes mellitus, humans with hypertension-induced cardiac hypertrophy have decreased myocardial uptake, utilization, and oxidation of fatty acid compared with controls, as demonstrated by PET [21]. This is similar to observations in animal models [22]. Whether there is an increase in myocardial glucose utilization in humans with hypertension is not known.

Myocardial substrate metabolism in hyperlipidemia

Animal models and coronary arterial–venous balance studies in humans have shown that triglycerides are a fuel for the myocardium and that, if their delivery to the heart is increased, so is their myocardial metabolism [23]. There is little information evaluating this in humans by means of noninvasive imaging, however, and there are no studies on the effect of low concentrations of HDL cholesterol on myocardial metabolism. The net effect of the metabolic syndrome on myocardial metabolism in persons with insulin resistance, hypertension, and other components is probably determined by the degree and interaction of all components.

Conclusion

Many components of the metabolic syndrome are associated with abnormalities in myocardial energy metabolism that may contribute to decreased cardiac function. Noninvasive imaging modalities are being used to quantify myocardial substrate preferences, and the oxidation, storage and energetics of the substrates that are particular to the metabolic syndrome. The sum of the data from human studies of the effects of most of the components of the metabolic syndrome (except hypertension) suggest that there is an overdependence on and an increase in myocardial uptake, metabolism, and storage of fatty acid. Further development and application of cardiac metabolic imaging techniques to the metabolic syndrome will help to define novel therapeutic targets and assess their efficacy. ■

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