# Efficacy of the metabolic approach in ischemic heart diseases

## Non invasive assessment of myocardial perfusion, metabolism, and left ventricular function

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## Abstract

The differentiation between viable and non viable myocardium is an important diagnostic issue in patients with coronary artery disease. Ischemic heart disease is a metabolic disease in which dysfunctional myocardium may recover contractility as a consequence of inhibition of fatty acid oxidation in favor of glucose oxidation. Imaging techniques have different characteristics that may be used in clinical practice in order to quantify changes in contractility and myocardial perfusion in response to such metabolic modulation. Trimetazidine – the metabolic agent for which there is the greatest scientific evidence base – has been shown to reduce the symptoms of angina and to improve left ventricular function through improvements in the contractility and perfusion of dysfunctional myocardium. The best results have been obtained in patients with viable myocardium, such as those with multiple coronary artery disease and diabetes mellitus.
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**Keywords:** Metabolic modulation, chronic myocardial ischemia, trimetazidine, dobutamine stress echocardiography, SPECT imaging

## Introduction

Coronary artery disease is the leading cause of death in the United States and Europe [1] and, despite the trend toward a decrease in incidence over the past 20 years, it still represents an heavy economic burden for all developed countries. Moreover, there is epidemiological and clinical evidence that, since 1990, coronary artery disease has become the most frequent cause of chronic heart failure. In the 21 multicenter congestive heart failure treatment trials involving 35 000 patients that have been reported by the *New England Journal of Medicine* over the past 15 years, the underlying cause of congestive heart failure was coronary artery disease in about 65% of patients [2].

The differentiation between viable and non viable myocardium is an important diagnostic issue in patients referred for revascularization. In fact, it has been estimated that between 25 and 40% of patients with chronic coronary artery disease and left ventricular dysfunction have the potential for significant improvement in systolic performance after undergoing revascularization [3]. Left ventricular ejection fraction may increase by up to 50% at 6 months after coronary artery bypass surgery [4], and this improvement is predicted by presurgical detection of viable myocardium [5]. Rahimtoola [6] coined the term 'hibernating myocardium' to describe a state of persistently impaired myocardial and left ventricular function at rest as a result of reduced coronary blood flow that can be partially or completely restored to normal by reducing demand or improving blood flow, or both.

In conditions of multiple coronary artery disease and left ventricular dysfunction, imaging techniques have clearly shown that cardiac impairment is caused, not only by the consequences of necrosis, but also by a different amount of viable dysfunctional myocardium that may surround the necrotic area or may be evident in distal territories served by other stenotic vessels (*Table I*).

Nuclear techniques and dobutamine stress echocardiography have been widely used in clinical practice.

*Table I. Comparison of technical and clinical aspects of non invasive imaging methods to detect myocardial viability.*

| Technique | Ionizing radiation | Contrast media | Spatial resolution (mm) | Imaging time | Tomographic capability | Strengths | Limitations |
|---|---|---|---|---|---|---|---|
| Dobutamine echocardiography | No | No | 2–3 | Real time | Yes | High specificity, good spatial resolution, good predictivity, widely available, no radiation | Poor window in 30% of patients, lower sensitivity, operator dependent |
| SPECT imaging | Yes | No | 10–15 | Minutes | Yes | High sensitivity after revascularization, quantitative assessment of perfusion and LVEF, predictivity of clinical outcome | Lower specificity than echocardiography, lower spatial resolution and specificity than PET |
| Positron emission tomography | Yes | No | 5–10 | Minutes | Yes | Higher specificity than SPECT, absolute blood flow quantification, predictive of clinical outcome | Lower specificity than echocardiography and MRI, no separation of endo- and epicardial viability, high cost |
| Magnetic resonance imaging | No | No | ~1 | Minutes | Yes | Higher spatial resolution than SPECT and dobutamine echocardiography, simultaneous assessment of perfusion, function and viability, wall thickness more accurate | Imaging not in real time, presence of metallic devices, high costs, limited availability |

LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Positron emission tomography has the advantage of evaluating myocardial metabolic activity in regions of underperfused and dysfunctional myocardium, using [$^{18}$F]-fluorodeoxyglucose (FDG) as a marker of regional utilization of exogenous glucose [7]. Regions with enhanced uptake of FDG relative to perfusion (mismatch) represent ischemic or hibernating myocardium, in which the preferential metabolic substrate shifts from fatty acid to glucose.

Metabolic activity in myocardial regions with reduced blood flow is an accurate clinical marker of viability, with mean sensitivity and specificity of 93% and 58%, respectively, and mean positive and negative predictive values of 71% and 86%, respectively [8]. Stunning is defined as a transient impairment of left ventricular function that persists after reperfusion. There is a perfusion–contraction mismatch as a result of repetitive bouts of demand ischemia in an area of myocardium served by a stenotic epicardial coronary artery that reduces flow reserve but not basal myocardial flow. Despite normal blood flow at rest, the inability of coronary flow to increase in parallel to increased demand (exercise or distress) may determine repeated episodes of myocardial ischemia, leading to chronic contractile dysfunction. In contrast to hibernation, the presence of stunning myocardium does not influence the clinical decision-making process, because the vessel supplying the stunned myocardium is already patent. Despite some peculiarities, the difference between stunning and hibernation seems to be more semantic than real, as overlapping clinical syndromes are more common. A reduction in coronary flow reserve is the common feature linking stunning and hibernation.

## Cellular fatty acid inhibition and left ventricular function: clinical evidence

In conditions of chronic reduction in blood flow, free fatty acid concentrations are increased as a result of the lipolytic action of sympathetic activation, causing depressed myocardial contractility, increased concentrations of cAMP, and increased oxygen consumption without concomitant increase in myocardial work [9]. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because ATP production per mole of oxygen required is greater

when glucose is the preferential substrate. In fact, the number of moles of ATP produced per mole of oxygen consumed is approximately 12% greater for glucose than for fatty acids. As fatty acid metabolism increases, glucose oxidation decreases, leading to uncoupling of glycolysis from glucose oxidation and an increase in proton and lactate production. This uncoupling increases the rate of pyruvate production without a concomitant increased rate of glucose oxidation in the mitochondria, generating cellular damage and contractile dysfunction. In this setting, the inhibition of fatty acid oxidation and the increased glucose oxidation may induce beneficial effects and may theoretically improve left ventricular function [10].

The most studied metabolic agent is *trimetazidine*, which inhibits the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [11]. Thus glucose oxidation is increased by shift of energy substrate preference from fatty acid to glucose oxidation [12]. As a result of this action, trimetazidine ensures antianginal and anti-ischemic efficacy and improves left ventricular function.

The effects of trimetazidine were studied in 38 patients with postnecrotic left ventricular dysfunction and multivessel coronary artery disease [13]. Patients were allocated randomly to two matched groups: one received trimetazidine 20 mg for 2 months, and the other received placebo. Treated patients exhibited significant improvements in systolic wall thickening score index (13% and 21%, at rest and in a stress test at peak dobutamine infusion, respectively; $P < 0.001$), in left ventricular ejection fraction (19.7% and 14.1%, at rest and in a stress test at peak dobutamine infusion, $P < 0.001$ [*Figure 1*]), and in peak oxygen consumption (15%). These benefits were obtained without concomitant changes in heart rate and blood pressure, suggesting that cytoprotection unrelated to hemodynamic effects is likely to occur. No side effects were observed among the treated patients. These findings are in agreement with those described by Brottier et al [14] in patients with ischemic cardiomyopathy, of a 9.3% improvement in radionuclide ejection fraction after a 6 month treatment with trimetazidine at the same dose. Left ventricular ejection fraction remained unchanged with trimetazidine at 3 months, and showed a mean improvement of 9.3% at 6 months. In contrast, patients receiving placebo experienced a 4.5% decrease in left ventricular ejection fraction at 3 months, and a further 15.6% deterioration at 6 months, as compared with baseline values ($P = 0.018$). Cardiac volume on chest X-ray remained stable in the two groups during the first 3 months, whereas at 6 months it had decreased significantly in the trimetazidine group compared with

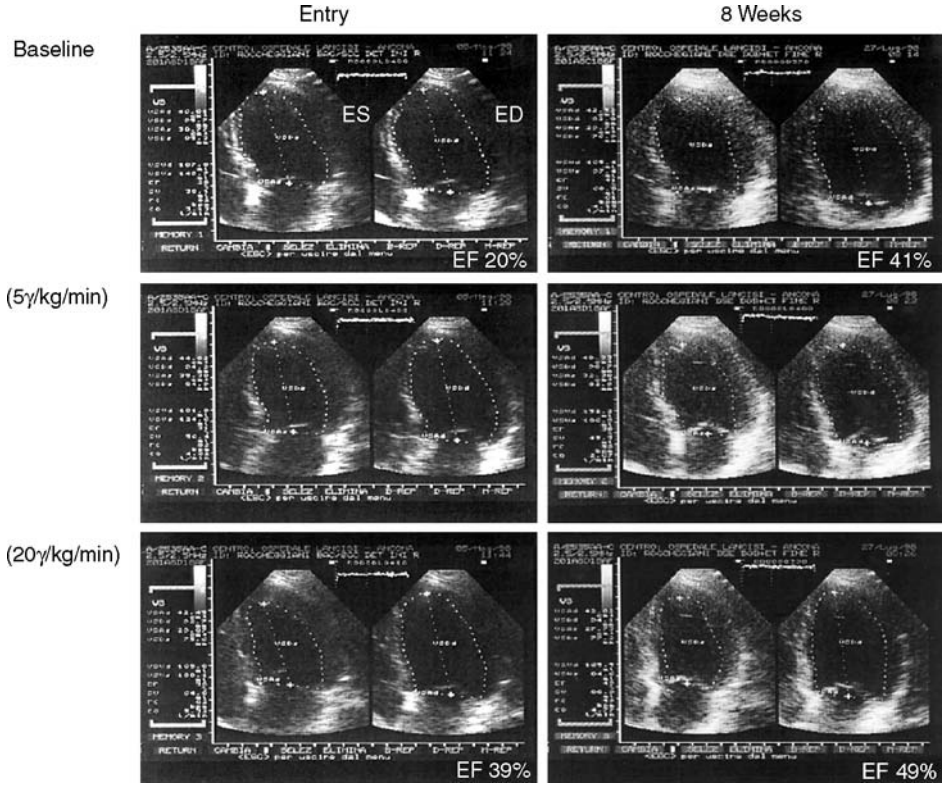


*Figure 1. Effects of trimetazidine on left ventricular contractility in a 56-year-old man with ischemic cardiomyopathy. The contractile response was evaluated with stress echocardiography (low-dose dobutamine: increasing by 5 μg/kg per min every 3 min, up 20 μg/kg per min) before and after 8 weeks of treatment. There was an improvement in the contractile response of septal segments, resulting in a greater ejection fraction at peak dobutamine infusion. ED, end-diastole; EF, ejection fraction; ES, end-systole.*

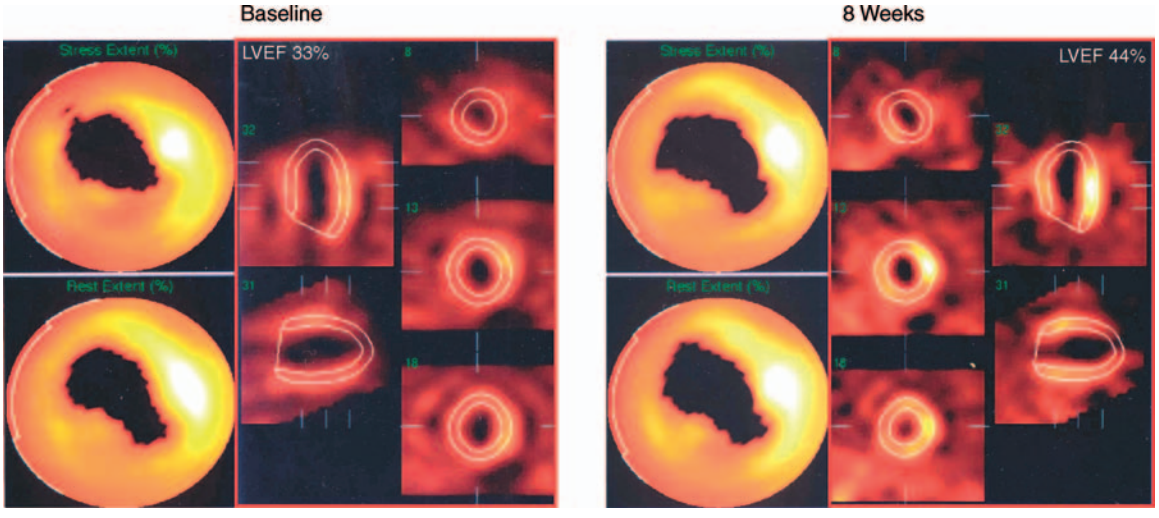


*Figure 2. Improvement in myocardial contractility after trimetazidine in a patient with ischemic cardiomyopathy. The patient was a 32-year-old man who had an anterior myocardial infarction 12 months before beginning treatment with trimetazidine for 8 weeks. At baseline, single photon emission computed tomography (SPECT) images, obtained after Bruce exercise stress testing followed by intravenous injection of 500 MBq tetrofosmin, showed a fixed defect (summed stress score (SSS) 22, summed difference score 3) in the apical region and left ventricular dysfunction (left ventricular ejection fraction [LVEF] 33%), with viable myocardium present in the area around the scar. Quantitative measurements of left ventricular volumes from gated perfusion SPECT images were obtained, from which ejection fraction was calculated automatically. At 8 weeks, despite no change in myocardial perfusion, there was a significant improvement in global left ventricular function (ejection fraction 44%) as a result of enhanced contractility of dysfunctional myocardium, particularly evident in short-axis images (right).*

those who received placebo ($P = 0.034$). Treated patients also had enhanced functional capacity, as shown by improvement in New York Heart Association (NYHA) functional class ($P < 0.001$).

The findings of these previous studies emphasized that major benefits are obtained with trimetazidine when hibernating/stunned myocardium is present. In fact, improvement in left ventricular function has been observed after the addition of trimetazidine to standard therapy in the human clinical model of ischemic cardiomyopathy with multivessel coronary artery disease and one or more cardiovascular risk factors (*Figures 2, 3*). This model is characterized by viable and non viable cells, with areas of hibernating/stunned dysfunctional myocardium mixed with necrotic and normal myocardium, fed by coronary arteries with multiple atherosclerotic lesions of different severity. The optimization of cellular energy metabolism by trimetazidine improves ATP resynthesis through the inhibition of fatty acid oxidation and stimulation of glucose oxidation. Diabetic patients with multiple coronary artery disease and dysfunctional myocardium have been studied in more detail, because this model is associated with metabolic and functional abnormalities susceptible to improvement after the addition of a metabolic modulator agent [15].

Diabetic patients have a greater incidence of coronary artery disease, which is in part related to concomitant cardiovascular risk factors such as hypertension, blood lipid abnormalities, obesity, and physical inactivity [16]. They have a greater incidence of mortality during and after an acute myocardial infarction, and a greater rate of complications, including left ventricular dysfunction and heart failure [17]. The main metabolic abnormality of the diabetic heart is the decreased ability to oxidize pyruvate as a consequence of phosphorylative inhibition of pyruvate dehydrogenase (PDH) resulting from upregulation of PDH kinase [18]. Infusions of glucose and insulin in patients after acute myocardial infarction resulted in

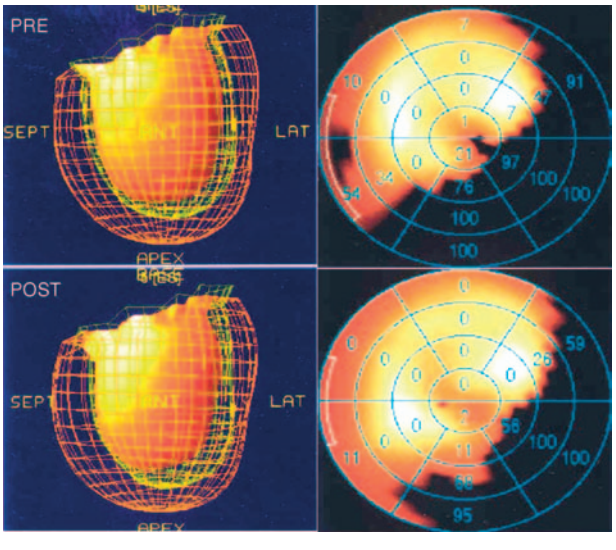


*Figure 3. Effects of trimetazidine in a 60-year-old man with ischemic cardiomyopathy. Left: Regional myocardial contractility improved at the anterolateral apical segment, resulting in a greater ejection fraction (increased from 32% before trimetazidine to 39% after the treatment). Right: Myocardial perfusion was only slightly improved (summed stress score (SSS) decreased from 24 to 22).*

a 29% reduction in mortality at 1 year as compared with conventional therapy [19]. This effect was more marked in patients with a low cardiovascular risk profile and any previous insulin treatment (52% reduction). These effects are attributed in most part to the reduction in plasma concentrations of free fatty acids and ketone bodies, resulting in less inhibition of PDH activity, less accumulation of lactate, and greater production of ATP.

Recently, we studied 34 clinically-stable patients (29 men, five women, mean age $54 \pm 9$ years, ejection fraction $38 \pm 6\%$ with diabetes mellitus and documented multivessel coronary artery disease [20]. Twenty-four patients had non-insulin dependent (type 2) diabetes mellitus (NIDDM), and 10 had insulin-dependent (type 1) diabetes mellitus (IDDM). Patients were allocated randomly to two groups: one group ($n = 19$) received trimetazidine for 3 months, and the other (controls; $n = 15$) received placebo during the same period. Medications were unchanged during the study. On study entry and at 3 months, all patients underwent gated-single photon emission computed tomography (SPECT) myocardial scintigraphy with a 2 day (Bruce) stress–rest protocol (500 MBq tetrofosmin). Quantitative measurements of left ventricular volumes from gated perfusion SPECT images were obtained, from which ejection fraction was calculated automatically. All patients completed the procedure, and no side effects were reported. On initial evaluation, there were no differences between the trimetazidine and control groups with respect to: severity of perfusion defects (summed difference scores $8.9 \pm 2.2$ and $8.6 \pm 2$, respectively); systolic wall thickening index (SWTI) ($2.2 \pm 0.8$ and $2.3 \pm 0.9$, respectively); left ventricular ejection fraction ($37 \pm 6\%$ and $38 \pm 6\%$, respectively). At 3 months, however, trimetazidine-treated patients exhibited significant improvement compared with control patients with respect to: SWTI ($1.7 \pm 0.9$ compared with $2.3 \pm 0.9$, respectively; $P < 0.05$) and left ventricular ejection fraction ($43 \pm 6\%$, compared with $38 \pm 6\%$, respectively; $P = 0.007$) (*Figure 4*). These results were similar in patients with type 1 or type 2 diabetes. No changes were observed in myocardial defects (summed difference scores $8.2 \pm 2.4$ in the trimetazidine group and $8.9 \pm 2.1$ in the control group; $P = 0.38$). Total exercise time was also improved in patients treated with trimetazidine (from $440 \pm 140$ s to $530 \pm 145$ s; $P < 0.05$), whereas no change was observed in controls. We conclude that, in patients with diabetic cardiomyopathy, trimetazidine improves left ventricular systolic function and functional capacity without significant changes in myocardial defects, suggesting that a direct cytoprotective effect on myocardial cells may translate into improvements in contractility of dysfunctional myocardium and functional capacity.

Metabolic modulation is able to improve, not only contractility of dysfunctional myocardium, but also diastolic filling, and these beneficial effects translate into improvements in left ventricular function and functional capacity in patients with ischemic cardiomyopathy with or without diabetes.

In one study, Fragasso et al [21] studied the effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. Sixteen male patients were allocated randomly to groups to receive either placebo or trimetazidine orally for 15 days, followed by a 6 month treatment, according to a double-blind crossover design. Both at 2 weeks and at 6 months, ejection fraction had improved significantly in treated patients ($P < 0.001$ compared with placebo for both), whereas endothelin-1 concentrations decreased ($P < 0.001$ at 2 weeks and $P = 0.03$ at 6 months). Fasting blood

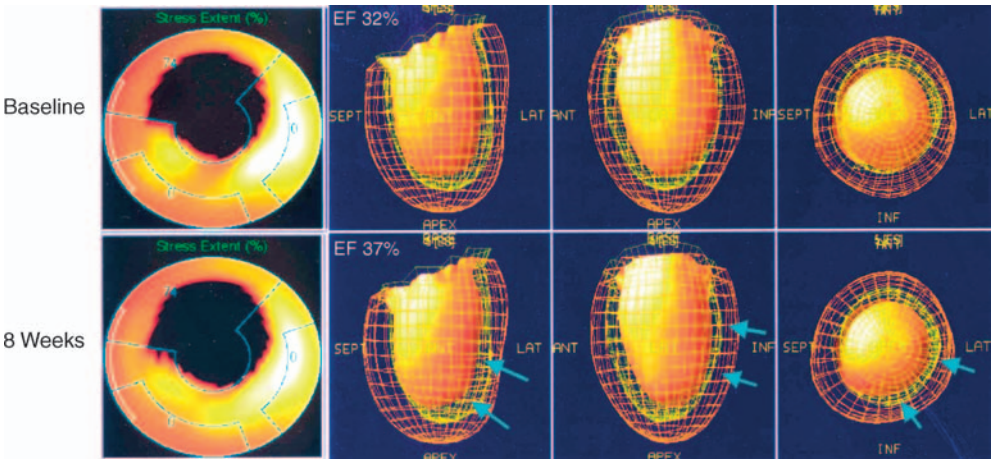


*Figure 4. Improvement in myocardial contractility without change in perfusion after trimetazidine for 8 weeks in a 50-year-old man with ischemic cardiomyopathy and type 2 (non-insulin-dependent) diabetes mellitus in a stable condition. At 8 weeks, there were no changes in myocardial perfusion compared with baseline (a severe fixed defect in the inferolateral wall is evident at baseline and at 8 weeks). However, there was a 16% improvement in global left ventricular function (ejection fraction 37%) as a result of enhanced contractility of dysfunctional myocardium (arrows). EF, ejection fraction.*

glucose also decreased significantly after 2 weeks ($P = 0.02$), but no significant change was observed at 6 months. At 2 weeks, 10 of the 16 patients had improved their NYHA functional class by 1 ($P = 0.019$ compared with placebo), and eight patients maintained the improvement at 6 months ($P = 0.018$ compared with placebo). In summary, trimetazidine improved left ventricular function, NYHA functional class, glucose metabolism, and endothelial function in patients with diabetes and ischemic cardiomyopathy. Similar results were observed more recently in 32 patients (24 men, eight women, mean age $67 \pm 6$ years) with type 2 diabetes and ischemic cardiomyopathy (ejection fraction 32%) who were allocated randomly to groups to receive trimetazidine or placebo for 6 months. Left ventricular ejection fraction increased by $5.4 \pm 0.5\%$ in patients receiving trimetazidine ($P < 0.05$) in relation to significant decreases in left ventricular end-diastolic and end-systolic volumes (decreases of 8% and 17%, respectively; $P < 0.05$ for both parameters compared with placebo). Significant improvements in wall motion score index and diastolic filling mitral inflow pattern (E/A ratio) were also observed only in treated patients.

In a more recent study, the same authors found improvements in left ventricular function in 47 elderly patients aged $78 \pm 3$ years with coronary artery disease who were treated with trimetazidine at doses of 20 mg three times daily in addition to standard therapy for 6 months [22]. Similar to previously reported findings, both left ventricular systolic and diastolic function were improved, in addition to NYHA functional class.

## Summary

Ischemic heart disease is a metabolic disease in which dysfunctional myocardium may recover contractility as a consequence of inhibition of fatty acid oxidation in favor of glucose oxidation. Thus the metabolic approach with trimetazidine, beyond its well demonstrated antianginal efficacy, leads also to a significant improvement in left ventricular function.

Imaging techniques have different characteristics that may be utilized in clinical practice to quantify changes in contractility and myocardial perfusion after metabolic modulation. Both low-dose dobutamine echocardiography and thallium/tetrofosmin SPECT imaging have been utilized in studies in which left ventricular dysfunction improved after the administration of trimetazidine, showing a good diagnostic accuracy in detecting changes compared with baseline during follow-up studies. Positron emission tomography images have greater spatial resolution and specificity than SPECT, but the high costs and limited availability of the technique have hampered its clinical application in studies on metabolic modulation. ■

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