

Featured research

Abstracts and commentaries

Relation between the assessment of microvascular injury by cardiovascular magnetic resonance and coronary Doppler flow velocity measurements in patients with acute anterior wall myocardial infarction

Hirsch A, Nijveldt R, Haeck JD, et al. *J Am Coll Cardiol.* 2008;51:2230–2238.

To assess myocardial reperfusion in patients with acute anterior myocardial infarction treated by primary percutaneous coronary intervention (PCI), the relationship between the presence and severity of microvascular obstruction was studied, using cardiovascular magnetic resonance (CMR) and intracoronary Doppler flow measurement. CMR has been used to detect and quantify microvascular obstruction in patients after acute myocardial infarction, but has never been compared with coronary blood flow velocity patterns. Twenty-seven patients with first anterior ST-segment elevation myocardial infarction successfully treated with primary PCI were included. Coronary blood flow velocity was measured during re-catheterization 4–8 days after primary PCI. These measurements were related to microvascular obstruction determined by late gadolinium-enhanced CMR performed the day before re-catheterization. Early systolic retrograde flow was observed in none of eight patients without microvascular obstruction on late gadolinium-enhanced CMR, and in 10 of 19 patients (53%) with microvascular obstruction ($P=0.01$). The extent of microvascular obstruction correlated with the diastolic:systolic velocity ratio ($r=0.44$; $P=0.02$), diastolic deceleration time ($r=-0.61$; $P=0.001$), diastolic deceleration rate ($r=0.75$; $P<0.0001$), and coronary flow velocity reserve of the infarct-related artery ($r=-0.44$; $P=0.02$). Furthermore, multivariate regression analyses, including extent of microvascular obstruction, infarct size, and transmural necrosis on late gadolinium-enhanced CMR, revealed that the extent of microvascular obstruction was the only independent factor related to early systolic retrograde flow and diastolic deceleration rate. It was concluded that the assessment of microvascular injury by late gadolinium-enhanced CMR corresponds well to evaluation by intracoronary Doppler flow measurements. By means of CMR, quantification of myocardial function, infarct size, and microvascular injury can be performed accurately with a single non invasive technique in patients with acute myocardial infarction.

Commentary

The reperfusion of an ischemic area with oxygenated blood may cause severe and irreversible microvascular damage, resulting in adverse electrical, functional, and biochemical effects, together known as the “no-reflow” phenomenon. It has been shown that the occurrence of no-reflow in humans after acute myocardial infarction is associated with less good prognosis and worse left ventricular remodeling. The no-reflow phenomenon can be detected invasively, at the time of primary PCI, by the Thrombolysis In Myocardial Infarction (TIMI) frame count or by intracoronary Doppler ultrasound. Coronary microvascular damage can also be assessed non invasively by contrast echocardiography, nuclear medicine, and cardiovascular magnetic resonance. Both the invasive and the non invasive approaches apply the term no-reflow, referring to the same pathophysiologic event, namely microvascular obstruction, but they look at this event at different times, with different modalities, and different sensitivities.

Coronary magnetic resonance appears to be the most efficient and sensitive method of detecting microvascular damage, even when compared with the invasive approaches. However, the no-reflow phenomenon is an extremely dynamic process. Investigations taken at different times may give conflicting indications, independent of the investigational technique, as a consequence of the dynamic nature of the event or of treatments received by the patient, or both. It should also be considered that the no-reflow phenomenon varies widely in severity from patient to patient, most often with progressive worsening in the first 48 h, but sometimes improving with time. Moreover, studying the no-reflow with cardiac magnetic resonance is strongly affected by the technique chosen. Given the rapid diffusion into the normal interstitial space and in the area of microvascular damage, the distribution of gadolinium-based contrast changes in size over time. Thus the magnitude of the damaged area is affected by the timing of acquisition of the image after injection of the contrast. Other sequences, including gradient-echo with or without an inversion-recovery preparatory pulse, may have better spatial resolution. First-pass perfusion can present defects resulting from previous infarctions, or other flow abnormalities. Adjustments of the T1 time may also affect the size of the damaged myocardium.

The lack of a gold standard to define the area of microvascular damage is a major limitation to the development of strategies that focus more on myocardial perfusion than on vessel recanalization. An accurate assessment of the area at risk for reperfusion damage (no-reflow) would open an opportunity to test potential therapies.

Mario Marzilli

Malonyl coenzyme A decarboxylase regulates lipid and glucose metabolism in human skeletal muscle

Bouzakri K, Austin R, Rune A, et al. *Diabetes*. 2008;57:1508–1516.

Malonyl coenzyme A (CoA) decarboxylase (MCD) is a key enzyme responsible for malonyl CoA turnover and functions in the control of the balance between lipid and glucose metabolism. Gene silencing based on RNA interference (small interfering RNA [siRNA]) was used to determine the direct role of MCD in the metabolic responses in primary human skeletal muscle, silencing *MCD* gene expression in cultured human myotubes from healthy volunteers (seven men and seven women) with no known metabolic disorders. Thereafter, lipid and glucose metabolism and signal transduction were determined under basal and insulin-stimulated conditions. RNA interference-based silencing of *MCD* expression (75% reduction) increased malonyl CoA concentrations 2-fold and shifted substrate utilization from lipid to glucose oxidation. RNA interference-based depletion of *MCD* reduced basal oxidation of palmitate. In parallel with this reduction, palmitate uptake was decreased under basal (40%) and insulin-stimulated (49%) conditions, compared with that in myotubes transfected with a scrambled sequence. Furthermore, *MCD* silencing increased basal and insulin-mediated glucose oxidation 1.4- and 2.6-fold, respectively, compared with that in myotubes transfected with a scrambled sequence. In addition, glucose transport and cell-surface glucose transporter-4 content were increased. In contrast, the action of insulin on insulin receptor substrate-1 tyrosine phosphorylation, tyrosine-associated phosphatidylinositol 3-kinase activity, Akt, and glycogen synthetase kinase phosphorylation was unaltered in myotubes transfected with siRNA against *MCD* compared with those transfected with a scrambled sequence. These results provide evidence that *MCD* silencing suppresses lipid uptake and enhances glucose uptake in primary human myotubes. It was concluded the expression of *MCD* has a key

reciprocal role in the balance between lipid and glucose metabolism.

Commentary

Exposure of muscle (skeletal muscle or heart) to high concentrations of fatty acids is associated with a decrease in the ability of insulin to stimulate glucose uptake and metabolism (ie, insulin resistance). The accumulation of cytoplasmic fatty acid intermediates such as diacylglycerol, triacylglycerol, and ceramides may contribute to an impairment of insulin signaling in the muscle. Therapeutic strategies that decrease the exposure of muscle to fatty acids (ie, that decrease blood fatty acid concentrations) can help improve the sensitivity of muscle to insulin. However, the role of mitochondrial fatty acid oxidation in mediating skeletal muscle insulin resistance is controversial. Inhibiting fatty acid oxidation has the potential to increase muscle uptake of glucose, glycolysis, and glucose oxidation (by the Randle Cycle effect), thereby having an insulin-sensitizing effect. However, it has also been proposed that stimulating fatty acid oxidation can have an insulin-sensitizing effect, secondary to decreasing the cytoplasmic concentration of lipids that can inhibit insulin signaling (such as diacylglycerols).

An important regulator of fatty acid oxidation in muscle is malonyl CoA, which is a potent inhibitor of mitochondrial fatty acid uptake. Malonyl CoA concentrations, in turn, are regulated by malonyl CoA decarboxylase (*MCD*), which degrades malonyl CoA. As a result, inhibition of *MCD* should increase malonyl CoA concentrations and inhibit fatty acid oxidation. The study by Bouzakri K et al examined what effect inhibition of *MCD* in human skeletal muscle cells has on insulin sensitivity. Using an siRNA approach in human skeletal muscle cells, the authors showed that decreasing *MCD* activity results in an increase in malonyl CoA concentrations and a decrease in rates of fatty acid oxidation. Accompanying the decrease in fatty acid oxidation was an increase in insulin-stimulated glucose transport and glucose oxidation. Inhibition of fatty acid oxidation was also associated with an increase in insulin-stimulated glucose transporter-4 present on the surface of the muscle cells. This is a very important finding, because it suggests that inhibition of fatty acid oxidation (as opposed to stimulation of fatty acid oxidation) has an insulin-sensitizing effect in human skeletal muscle. It also suggests that fatty acid oxidation inhibitors have potential therapeutic benefit in the treatment of insulin resistance and diabetes.

Gary D. Lopaschuk
