

Featured research

Abstracts and commentaries

Fatty acid transporter levels and palmitate oxidation rate correlate with ejection fraction in the infarcted rat heart

Heather LC, Cole MA, Lygate CA, et al. *Cardiovasc Res* 2006;72:430–437.

Changes in fatty acid metabolism have been detected in various models of cardiac hypertrophy and failure. In heart failure, many mitochondrial β -oxidative enzymes have reduced activity, and are partly responsible for the overall decrease in fatty acid metabolism. However, it is plausible that decreased sarcolemmal fatty acid uptake may limit entry of the fatty acid moieties into the β -oxidation cycle and thus contribute to the downregulation of this pathway. Cardiac free fatty acid uptake occurs predominantly via sarcolemmal transporter proteins: fatty acid translocase (FAT/CD36), plasma membrane fatty acid binding protein (FABPpm) and fatty acid transporter proteins (FATP) 1 and 6. The significance of these proteins in fatty acid metabolism has been highlighted using knockout models in which cardiac fatty acid uptake and oxidation were significantly impaired. In this study, the authors hypothesized that concentrations of the fatty acid transporters would be reduced in the chronically infarcted rat heart, in parallel with reduced dependence on fatty acid utilization. This hypothesis was tested by examining several stages of the fatty acid utilization process, from the protein concentrations of the fatty acid transporters to fatty acid oxidation and rates of lipid incorporation.

Commentary

In vivo left ventricular ejection fractions, measured using echocardiography, were 36% smaller in rats 6 months after coronary artery ligation than in sham-operated control rats. In isolated, perfused, infarcted hearts, palmitate oxidation rates were 30% lower and correlated positively with in vivo ejection fractions. As

myocardial lipid incorporation was also reduced by 25%, total palmitate utilization was 29% lower in the infarcted rat heart. In addition, a novel observation in this study was the reduction in the concentrations of fatty acid transporter in the failing heart. Protein concentrations were lower, with decreases of 36% for FAT/CD36, 26% for FATP1, 21% for FATP6, and 12% for FABPpm. It is of note that lower fatty acid transporter concentrations in the infarcted rat hearts correlated with both palmitate oxidation rates and cardiac ejection fractions. In addition, concentrations of cytosolic fatty acid binding protein, the protein probably responsible for shuttling the fatty acid moieties from the sarcolemma to the mitochondria for oxidation, were also markedly decreased. Finally, medium-chain acyl-coenzyme A dehydrogenase activity, a marker of mitochondrial β -oxidative capacity, was significantly reduced after myocardial infarction compared with that in sham hearts. Thus the decrease in fatty acid transporter concentrations in the failing hearts may well account for the decrease in fatty acid utilization by restricting entry of fatty acids to the cardiomyocyte.

Together, these findings showed that the transition away from fatty acid metabolism correlated with the degree of myocardial impairment, in that those hearts with the smallest ejection fractions oxidized the smallest proportion of fatty acids. In the normal healthy heart, 70–90% of fatty acids is diverted to oxidation, and 10–30% is incorporated into the cardiac tissue. It was also shown that, in addition to the reduced rates of palmitate oxidation, myocardial lipid incorporation was reduced in the infarcted rat hearts. This may indicate a depletion of intracellular substrate reserves which, in turn, may jeopardize the ability of the heart to generate sufficient energy during times of increased metabolic demand. It is also possible that the decrease in fatty acid transporters is important in the metabolic switch from fatty acid to carbohydrates in heart failure.

Danielle Feuvray

Coronary endothelial dysfunction is associated with erectile dysfunction and elevated asymmetric dimethylarginine in patients with early atherosclerosis

Elesber AA, Solomon H, Lennon RJ, et al. *Eur Heart J*. 2006;27:824–831.

Coronary endothelial dysfunction (CED) precedes atherosclerosis and is associated with cardiovascular events. Both CED and erectile dysfunction are partly mediated by impairment in the nitric oxide pathway. Erectile dysfunction is associated with established coronary atherosclerosis, but its relationship with early coronary atherosclerosis and CED is unknown. This study was designed to test the hypothesis that CED is associated with erectile dysfunction in men with early coronary atherosclerosis. Moreover, the role of the nitric oxide synthase inhibitor, asymmetric dimethylarginine (ADMA), was investigated; ADMA is a novel endogenous competitive inhibitor of nitric oxide synthase and has been shown to be an independent marker for cardiovascular disease. Fifty-six men without obstructive coronary artery disease who underwent coronary endothelial function testing were studied. ADMA concentrations were determined and all men were asked to complete the International Index of Erectile Function-5 questionnaire to assess erectile function. Patients were divided according to the presence ($n = 32$) or absence ($n = 24$) of CED. Men with CED had significant impairment of erectile function ($P = 0.008$) and significantly greater ADMA concentrations (0.50 ± 0.06 ng/mL compared with 0.45 ± 0.07 ng/mL, $P = 0.017$) compared with men with normal endothelial function. Erectile function correlated positively with coronary endothelial function. This correlation was independent of age, body mass index, high-density lipoprotein, C-reactive protein, homeostasis model assessment of insulin resistance index, and smoking status. It was concluded that CED is independently associated with erectile dysfunction and plasma ADMA concentration in men with early coronary atherosclerosis. This study further supports the role of the endothelium in systemic vascular diseases and the role of ADMA in the systemic manifestations of endothelial dysfunction.

Commentary

Erectile function is dependent on the production of nitric oxide and erectile dysfunction is associated with a reduction in nitric oxide production, usually secondary to endothelial dysfunction. Asymmetric dimethylarginine (ADMA) is derived from the degradation of methylated proteins and is found in plasma. It inhibits nitric oxide synthase, reduces nitric oxide concentrations, and is associated with cardiovascular

events. ADMA concentrations are 10-fold greater inside endothelial cells and have been shown to correlate with the degree of atherosclerosis in patients with coronary artery disease, chronic renal disease, and diabetes. Increased concentrations of ADMA in men with erectile dysfunction correlate with some cardiovascular risk factors, including markers of inflammation and lipoprotein (a), supporting the role of the endothelium in systemic vascular disease, including erectile dysfunction. Measuring ADMA may complement other aspects of establishing cardiovascular risk in men with erectile dysfunction and no cardiac symptoms, acting as a biochemical marker integrating cardiovascular risk factors with endothelial dysfunction.

Graham Jackson

A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure

Fragasso G, Pallosi A, Puccetti P, et al. *J Am Coll Cardiol*. 2006;48:992–998.

This study sought to assess whether the long-term addition of trimetazidine to conventional treatment could improve functional class, exercise tolerance, and left ventricular function in patients with heart failure. Previous small studies have shown that trimetazidine may be beneficial in terms of preservation of left ventricular function and control of symptoms in patients with postischemic heart failure. Fifty-five patients with heart failure were randomly allocated in an open-label fashion to either conventional therapy plus trimetazidine 20 mg three times daily (28 patients) or conventional therapy alone (27 patients). Mean follow-up was 13 ± 3 months. At study entry and at follow-up, all patients underwent exercise testing and 2-dimensional echocardiography. Among other parameters, New York Heart Association (NYHA) functional class and ejection fraction were evaluated. In the trimetazidine group, NYHA functional class improved significantly compared with the conventional therapy group ($P < 0.0001$). Treatment with trimetazidine significantly decreased left ventricular end-systolic volume (from 98 ± 36 ml to 81 ± 27 ml, $P = 0.04$) and increased ejection fraction (from $36 \pm 7\%$ to $43 \pm 10\%$, $P = 0.002$). In contrast, in the conventional therapy group, both left ventricular end-diastolic and end-systolic volumes increased (from 142 ± 43 ml to 156 ± 63 ml, $P = 0.2$, and from 86 ± 34 ml to 104 ± 52 ml, $P = 0.1$, respectively); accordingly, ejection fraction decreased significantly

(from $38 \pm 7\%$ to $34 \pm 7\%$, $P=0.02$). In conclusion, long-term treatment with trimetazidine improves functional class and left ventricular function in patients with heart failure. This benefit contrasts with the natural history of the disease, as shown by the decrease in ejection fraction in patients receiving standard heart failure therapy alone.

Commentary

Trimetazidine is a fatty acid oxidation inhibitor that is clinically used in more than 90 countries for the treatment of angina pectoris. By inhibiting the fatty acid β -oxidation enzyme, 3-ketoacyl coenzyme A thiolase, trimetazidine inhibits cardiac fatty acid oxidation, resulting in a stimulation of glucose oxidation. This increase in glucose oxidation can improve the coupling of glycolysis to glucose oxidation, thereby decreasing ischemia-induced production of protons and increasing cardiac efficiency. Whether a similar approach can have therapeutic benefit in heart failure has not been studied extensively. One of the potential problems with this approach is that overall mitochondrial oxidative metabolism is decreased in heart failure, including fatty acid oxidation. However, to compensate, an increase in glycolysis occurs, which can add to the proton load of the heart and has the potential to decrease cardiac efficiency. The question

therefore arises as to whether decreasing fatty acid oxidation further, which increases glucose oxidation and can lessen proton production, can benefit the failing heart.

This study by Fragasso and colleagues would suggest that inhibition of fatty acid oxidation can benefit the patient with heart failure. Long-term treatment of such patients with trimetazidine resulted in an improved heart failure functional class and an improved left ventricular function. The study is supported by the findings of a number of previous smaller clinical trials showing that a variety of partial fatty acid oxidation inhibitors, such as trimetazidine, etomoxir, and perhexilene, can be of benefit to patients with heart failure. These observations are also supported by experimental studies showing that these fatty acid oxidation inhibitors and others (ranolazine and oxfenicine) also benefit the failing heart. The study by Fragasso and colleagues is important in that it describes a novel approach to the treatment of heart failure. It is also important in that it supports the concept that, even though mitochondrial oxidative metabolism can be impaired in heart failure, switching residual oxidative metabolism from fatty acid oxidation to glucose oxidation may be a novel approach to treating heart failure.

Gary Lopaschuk
