Featured research

Abstracts and commentaries

Nuclear receptors PPARβ/δ and PPARα direct distinct metabolic regulatory programs in the mouse heart

Burkart EM, Sambandam N, Han X, et al. J Clin Invest. 2007;117:3930–3939.

Diabetes predisposes to heart failure, particularly in combination with other comorbid conditions such as hypertension and coronary artery disease. Evidence has emerged that derangements in cardiac fuel metabolism, related to insulin-resistant and diabetic states, contribute to the development of diabetic cardiac dysfunction. The metabolic derangements in the diabetic heart involve gene regulatory programming via chronic activation of the nuclear receptor, peroxisome proliferator activated receptor α (*PPARα*). Chronic activation of the PPARα pathway drives excessive fatty acid oxidation, lipid accumulation, reduced glucose utilization, and cardiomyopathy. PPARα is a member of a fatty-acid-activated nuclear receptor family that includes PPARγ and PPARβ/δ. In contrast to PPARγ, which is expressed at low levels, PPARβ/δ is highly expressed in cardiac myocytes, similar to PPARα. The function of PPARα has been the subject of intense investigation; however, less is known about PPARβ/δ. To investigate the role of PPARβ/δ in the regulation of heart metabolism and function, the authors generated transgenic mice with cardiac-specific expression of PPARβ/δ driven by the myosin heavy chain (MHC-PPARβ/δ mice).

Commentary

The normal adult heart satisfies its energy requirements through the oxidation of both fatty acids and glucose. However, myocardial insulin resistance and increased rates of systemic lipolysis force the diabetic heart to rely almost exclusively on fatty acid as a fuel source – a loss of substrate flexibility. Over the long term, high rates of myocardial fatty acid utilization predispose to the development of a ''lipotoxic'' form of cardiomyopathy, characterized by accumulation of lipid in the myocytes, mitochondrial dysfunction, and generation of reactive oxygen species related to excessive substrate flux. In addition, the diabetic heart has a reduced capacity for glycolysis and glucose oxidation, which predisposes to postischemic damage. Recent evidence has implicated dysregulation of the nuclear receptor PPARα in the metabolic and functional derangements of the diabetic heart. PPARα activates transcription of genes involved in cellular pathways of lipid utilization, including fatty acid uptake and oxidation. The *PPARα* gene regulatory pathway is chronically activated in the hearts of insulin-deficient and insulin-resistant rodents. Transgenic mice with cardiac-specific overexpression of PPARα (MHC-PPARα mice) display a functional and metabolic phenotype that mimics the diabetic heart; specifically, MHC-PPARα mouse hearts exhibit increased rates of fatty acid oxidation, decreased glucose utilization, myocyte accumulation of triglyceride, and cardiomyopathy. Interestingly, the lipotoxic cardiomyopathy of MHC-PPARα mice is worsened with consumption of a high-fat diet. Consistent with observations in animal models, recent studies using positron emission tomography have shown that hearts of diabetic humans exhibit increased fatty acid uptake and utilization rates.

In the study by Burkart and colleagues, the authors describe the surprising finding that, in contrast to MHC-PPARα mice, MHC-PPARβ/δ mice did not develop myocyte accumulation of lipid or cardiomyopathy, even in the context of a high-fat diet. One likely explanation for this striking difference is that myocardial fatty acid uptake and esterification rates were increased in MHC-PPARα mice, but not in MHC-PPARβ/δ mice. The expression of genes involved in fatty acid uptake and triglyceride synthesis was activated in the hearts of MHC-PPARα mice, but not in MHC-PPARβ/δ mice. This differential gene regulation was also noted when PPARα and PPARβ/δ agonists were administered to wild-type mice. Collectively, these results suggest that the striking differences in

cardiac lipid metabolic phenotype exhibited by PPARα mice compared with PPARβ/δ transgenic mice are related to differential activation of a subset of gene-regulatory programs driving cellular transport and utilization of fatty acid. In striking contrast to MHC-PPARα mice, MHC-PPARβ/δ mice had increased myocardial glucose utilization, did not accumulate myocardial lipid, and had normal cardiac function. Consistent with these observed metabolic phenotypes, it was found that expression of genes involved in cellular fatty acid transport was activated by PPARα, but not by PPARβ/δ. Conversely, cardiac glucose transport and glycolytic genes were activated in MHC-PPARβ/δ mice, but repressed in MHC-PPARα mice. Furthermore, myocardial injury after coronary artery occlusion was significantly reduced in the MHC-PPARβ/δ mice compared with control or MHC-PPARα mice, consistent with an increased capacity for myocardial glucose utilization.

These results demonstrate that PPARα and PPARβ/δ drive distinct cardiac metabolic regulatory programs in the mouse heart, and identify *PPAR*β/δ as a crucial target for metabolic modulation therapy. If the same proves true in humans, selective activation of *PPAR*β/δ may then offer a potential therapeutic strategy for diabetic cardiac dysfunction.

Danielle Feuvray

Cardiac-resynchronization therapy in heart failure with narrow QRS complexes

Beshai JF, Grimm RA, Nagueh SF, for the RethinQ Study Investigators. N Engl J Med 2007;357:2461–2471.

Indications for cardiac resynchronization therapy (CRT) in patients with heart failure include a prolonged QRS interval (≥120 ms), in addition to other functional criteria. Some patients with narrow QRS complexes have echocardiographic evidence of left ventricular mechanical dyssynchrony and may also benefit from CRT. We enrolled 172 patients who had a standard indication for an implantable cardioverter-defibrillator. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for 6 months. The primary endpoint was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 mL per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary endpoint (46% and 41%, respectively). In a prespecified subgroup with a QRS interval of 120 ms or more, the peak oxygen consumption increased in the CRT group ($P=0.02$); it was unchanged in a subgroup with a QRS interval less than 120 ms ($P=0.45$). There were 24 heart-failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%); this difference was not significant. We conclude that CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT. (ClinicalTrials.gov number, NCT00132977 [ClinicalTrials.gov].). Copyright 2007 Massachusetts Medical Society.

Commentary

Cardiac resynchronization therapy has been shown to improve survival and quality of life in patients with heart failure with a prolonged Q–T interval. Since the introduction of CRT, two conflicting observations have emerged: a fraction of patients presenting with large QRS complexes do not benefit from this treatment, and patients with narrow QRS complexes may present mechanical dyssynchrony. The study by Beshai and colleagues is the first prospective, controlled, double-blind randomized trial to evaluate CRT in patients with heart failure with a narrow QRS complexes and evidence of mechanical dyssynchrony at echocardiography. The conclusion was that CRT did not improve peak oxygen consumption (the primary endpoint) or other secondary endpoints, including quality-of-life scores and left ventricular volumes. Possible reasons for these disappointing results may relate to the echocardiographic methods applied to detect dyssynchrony, or to lead placement, or both, but may be the consequence of a simplistic approach to the problem. Mechanical dyssynchrony – that is, a disparity in regional contraction timing – may be secondary to electrical dyssynchrony or may express regional muscle dysfunction. Dyssynchrony may be limited to systole or may extend to diastole. The more sophisticated the echocardiographic methods used, the more frequent is dyssynchrony in patients with systolic or diastolic heart failure, whether with narrow or with large QRS complexes. The clinical significance of these observations is not always obvious. However, applying CRT to all patients presenting with mechanical dyssynchrony at echocardiography, independent of knowledge of the pathogenetic mechanism, would expose to risk a growing number of non responders.

Mario Marzilli