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CARDIAC METABOLISM IN PHYSIOLOGICAL AND PATHOLOGICAL STATES AND OPPORTUNITIES OF METABOLIC INTERVENTION

M . Gurevich*

Department for Postgraduate Education,
Moscow Regional Scientific-Research Clinical Institute,

Abstract

Myocardial energetic disregulations in patients with heart failure contribute to myocardial dysfunction and to the progression of left ventricular remodeling. Discovering new pharmacologic agents which influence metabolic disturbances in myocardial dysfunction seems an attractive approach.

The article discusses the metabolic changes that occur in cardiac dysfunction , the consequences of these changes for cardiac metabolism and possible therapeutic metabolic interventions in heart failure.

Among metabolic agents there is clinical evidence that 3-KAT inhibitor trimetazidine may have a beneficial role in coronary disease and heart failure.

Keywords: cardiac metabolism, trimetazidine, systolic function, chronic heart failure

Introduction

Heart failure is defined as a "complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" [*Bristow M., 2000*]. Treatment of heart failure currently targets fluid overload and neurohormonal activation. Diuretics, digoxin, and inotropes treat fluid overload and improve hemodinamics; while angiotensin–converting enzime (ACE) inhibitors, angiotensin II receptor antagonists, beta-receptor antagonists and aldosterone antagonists suppress neurohurmoral activation. In spite of these treatments, there is still progression of contractile dysfunction and continuing left ventricular enlargement [*Colucci W.C. et al., 1996; Bristow M. et al., 1999; Coats A.J., 2002*].

Recent evidence has shown that more aggressive treatment with antagonists of neurohumoral activation in heart failure does not provide additional clinical benefit [*Colucci W.C. et al., 1996; Cottin Y. et al., 2002; Davila-Roman V.G. et al., 2002*], which allows to conclude that new approaches are needed for intervention on pathophysiologic and biochemical mechanisms of the development of chronic heart failure. Numerous studies showed that contractile dysfunction is caused by alterations in substrate metabolism. In particular, there is new evidence that in the failing heart a possibility to shift metabolism from a preference for fatty acids towards more carbohydrate oxidation can improve contractile function and slow the progression of pump failure [*Bristow M., 2000; Chandler M.P. et al., 2002; Stanley W.C., Chandler M.P., 2002*].

Energy production from the metabolism of glucose by heart involves two important parts, glycolysis and glucose oxidation. Most of glucose is derived from blood and glycolysis is the first step of reactions involved in the breakdown of glucose to pyruvate, which promotes small production of ATP (about 10% of all ATP produced by aerobic heart). This small production of ATP promotes to the ionic stability and cell composity. The second stage of glucose metabolism is glucose oxidation with the generation of pyruvate from glycolysis and lactate. Pyruvate is metabolized in mytochondria with the production of carbohydrate-derived ATP [*Wallhaus T.R. et al., 2001*].

In physiological state heart is able to use many energy substrates (fatty acids, glucose, lactate, ketones, amino acids), but mitochondrial

Addres for correspondense: *Department for Postgraduate Education, Moscow Regional Scientific-Research Clinical Institute*
58 Shchepkin Street, 117006, Moscow, Russia
Tel.: 007-495-681-03-03
E-mail: magurevich@hotmail.com

ATP is primarily produced by the oxidation of fatty acids and of pyruvate (derived from either glycolysis or lactate). The rate of metabolism along these different pathways is determined by arterial substrate concentration, hormones, coronary flow, inotropic state, and nutritional status [*Di Napoli R., et al., 2005*]. These effects are conditioned by different mechanisms and substrate-product relationships. In the normal heart, approximately 10-40% of the ATP is produced via pyruvate oxidation, whereas the remaining 60-90% is derived from the oxidation of fatty acids. An important enzyme link between carbohydrate oxidation and fatty acid metabolism is pyruvate dehydrogenase (PDH), which decarboxylates pyruvate to acetyl coenzyme A (CoA) [*Stanley W.C., Chandler M.P., 2002*].

Studies performed both in patients with heart failure and in animal models of heart failure show that there is a decrease of ATP content in tissue, an increase in ADP, and a decrease in the phosphorylation potential [*Di Napoli R. et al., 2005*], thus impairing the kinetics of ATP utilization of for cell contraction. In addition, heart failure impairs the capacity for the creatine kinase system to transfer mitochondrial ATP to the myofibril and decreases mitochondrial oxidative capacity, in part as a result of a decrease in electron transport chain activity [*Di Napoli R. et al., 2005*]. The electron transport chain defects in heart failure are consistent with the concept that, in heart failure, there is a major lesion in oxidative metabolism at the level of the chain. It appears that impairment in the electron transport chain reduces the in vivo capacity for myocardial generation of ATP and thus limits cardiac contractile function during high-level work, such as exercise or acute adrenergic stress. This is supported by studies in dogs with pacing-induced heart failure that reduced myocardial oxygen consumption in response to increased cardiac work was the result of a limitation of oxygen extraction, not of myocardial blood flow [*Wallhaus T.R. et al., 2001; Chandler M.P. et al., 2002; Nikolaidis L.A. et al., 2002*]. Data are consistent with the theory of impaired mitochondrial respiratory capacity in heart failure, resulting in reduced ability to generate ATP in response to increased demand for cardiac function. In support of this, recent studies have demonstrated that downregulation of the enzymes of fatty acid oxidation can be triggered by an abnormality in the electron transport chain in the mouse heart [*Hansson A. et al., 2004*].

In the early stages of heart failure, there is a normal or mildly increased rate of fatty acid oxidation, and in advanced heart failure there is downregulation of fatty acid oxidation. G. Paolisso et al. showed increased extraction and uptake of plasma free fatty acids and decreased glucose uptake in patients with congestive heart failure [*Paolisso G. et al., 1994*]. In patients with class II – III heart failure compared with healthy individuals a 60% decrease in cardiac carbohydrate oxidation was observed. Using positron emission tomography (PET), M. Taylor et al. found greater myocardial uptake of a radiolabeled fatty acid analog and less uptake of a radiolabeled deoxyglucose in patients with class III heart failure compared with those in healthy individuals [*Taylor M. et al., 2001*]. In contrast, patients with idiopathic dilated cardiomyopathy appear to exhibit the reverse: a greater myocardial glucose uptake and less fatty acid uptake compared with healthy subjects. Y. Yazaki et al. and V. Davila-Roman et al. found impaired utilization of fatty acids in patients with severe idiopathic dilated cardiomyopathy [*Yazaki Y. et al., 1999; Davila-Roman V.G. et al., 2002*]. It is important to note that, with PET, despite the possibility to estimate glucose uptake, it is not possible to make a direct measurement of the rate of glucose oxidation. It is therefore not clear from these studies whether flux through PDH is altered in these patients. To date, the limited availability of data on clinical investigations may be attributable to the severity of heart failure, supporting the idea that, in the early stages of heart failure, there is a normal (or slightly increased) rate of fatty acid oxidation with a dramatic downregulation of fatty acid oxidation in advanced or endstage heart failure.

Studies in animal models of heart failure like-

wise human studies suggest the increased or normal fatty acid oxidation in early heart failure and impaired fatty acid oxidation in severe heart failure. M. Chandler et al. measured myocardial substrate oxidation in dogs with well compensated microembolization-induced heart failure using isotopic tracers and found no differences in myocardial glucose, lactate, or fatty acid metabolism compared with those in normal dogs [*Chandler M. et al., 2004*]. In a canine rapid-pacing model of heart failure, F. Recchi et al. showed a relatively normal myocardial substrate metabolism in the early and middle stages of heart failure and a decrease in fatty acid oxidation in severe heart failure [*Recchi F.A. et al., 1998*]. In general, measurements of the level of expression of key enzymes in fatty acid oxidation support these direct measurements of energy metabolism [*Di Napoli R. et al., 2005*].

Pharmacological possibilities of the metabolic therapy of heart failure. The increased metabolism through free fatty acid pathway will inhibit the glycolytic way of metabolism, which is unfavourable in the decreased oxygen delivery to heart. Thus, the activation of PDH way glycolysis supposed to be an effective for improving cardiac metabolism and inhibiting possible metabolic injuries. There are several clinical data to support this concept. For instance, patients with classes II and III heart failure were infused with dichloroacetate [*Chandler M. et al., 2004; Hansson A. et al., 2004*], a compound that inhibits PDH kinase and thereby activates PDH and increases glucose oxidation. This resulted in an increase in stroke volume and ejection fraction, in addition to an improvement in cardiac efficiency. Increasing the plasma insulin concentration will also increase glucose oxidation and inhibit fatty acid oxidation.

Patients with ischemic heart disease and left ventricular dysfunction were treated with an infusion of insulin and showed an improvement in their wall motion scores and left ventricular ejection fraction [*Cottin Y. et al., 2002*]. Thus, in the short term, left ventricular function and mechanical efficiency are improved by the acute stimulation of myocardial carbohydrate metabolism and inhibition of fatty acid oxidation. This can be achieved by increasing activity at the level of PDH.

In long-term studies, patients with New York Heart Association (NYHA) classes II and III heart failure have been followed while receiving trimetazidine [*Fragasso G. et al., 2003; Rosano G.M. et al., 2003*] a fatty acid oxidation inhibitor. Two months of treatment resulted in significant improvement in left ventricular ejection fraction. Six months of treatment with trimetazidine improved diastolic function, whereas no change was observed in patients receiving placebo [*Fragasso G. et al., 2003; Rosano G.M. et al., 2003*]. A recent study by R. Di Napoli et al. [*Di Napoli R. et al., 2005*] also showed that in patients with NYHA classes II and III heart failure with ischemic dilated cardiomyopathy chronic treatment (up to 18 months) with trimetazidine can increase ejection fraction by 26-38%. More clinical trials are needed to prove the efficacy of trimetazidine in cardiac failure patients.

Another way of suppressing fatty acid oxidation is to inhibit carnitine palmitoyltransferase-1 (CPT-1). It has been shown that inhibiting CPT-1 with oxfenicine may prevent ventricular remodeling and slow the progression of heart failure in dogs [*Rupp H. et al., 1995; Rupp H., Vetter R., 2000*].

Conclusions

Optimizing energy metabolism in cardiovascular pathologies for management of both heart failure and coronary artery disease is the new approach. Pathophysiological and biochemical changes in chronic heart failure suggest that promotion of myocardial glucose metabolism can increase cardiac function and decrease the myocardial injury. A number of pharmacologic agents are now known to stimulate myocardial glucose oxidation directly or indirectly (by inhibition of fatty acid oxidation). However, among traditional pharmacologic agents there is clinical and investigational evidence that 3-KAT inhibitor trimetazidine may play an important role in therapy of chronic heart failure and coronary artery disease.

References

1. *Bristow M.R., Gilbert E.M., Abraham W.T., et al.* Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation. 1999; 94: 2807-2816.
2. *Bristow M.* Etomoxir: a new approach to treatment of chronic heart failure. Lancet 2000; 356:1621- 1622.
3. *Chandler M.P., Stanley W.C., Morita H., et al.* Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. Circ. Res. 2002; 91: 278-280.
4. *Chandler M.P., Kerner J., Huang H., et al.* Moderate severity heart failure does not involve a downregulation of myocardial fatty acid oxidation. Am. J. Physiol. Heart Circ. Physiol. 2004; 287: H1538-H1543.
5. *Coats A.J.* Angiotensin type-1 receptor blockers in heart failure. Prog. Cardiovasc. Dis. 2002; 44: 231-242.
6. *Colucci W.S., Packer M., Bristow M.R., et al.* Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation I. 1996; 94: 2800-2806.
7. *Cottin Y., Lhuillier I., Gilson L., et al.* Glucose insulin potassium infusion improves systolic function in patients with chronic ischemic cardiomyopathy. Eur. J. Heart Fail. 2002; 4: 181-184.
8. *Davila-Roman V.G., Vedala G., Herrero P., et al.* Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. J. Am. Coll. Cardiol. 2002; 40: 271-277.
9. *Di Napoli R., Taccardi A.A., Barossti A.* Long-term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomypopathy. Heart 2005; 91: 161-165.
10. *Fragasso G., Piatti P.M., Monti L., et al.* Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. Am. Heart J. 2003; 146: E18.
11. *Hansson A., Hance N., Dufour E., et al.* A switch in metabolism precedes increased mitochondrial biogenesis in respiratory chain-deficient mouse hearts. Proc. Natl Acad. Sci. USA. 2004; 101: 3136-3141.
12. *Nikolaidis L.A., Hentosz T., Doverspike A., et al.* Catecholamine stimulation is associated with impaired myocardial oxygen utilization in heart failure. Cardiovasc. Res. 2002; 53: 392-404.
13. *Paolisso G., Gambardella A., Galzerano D., et al.* Total-body and myocardial substrate oxidation in congestive heart failure. Metabolism. 1994; 43: 174-179.
14. *Recchia F.A., McConnell P.I., Bernstein R.D., Vogel T.R., Xu X., Hintze T.H.* Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. Circ. Res. 1998; 83: 969-979.
15. *Rosano G.M., Vitale C., Sposato B., Mercuro G., Fini M.* Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study. Cardiovasc. Diabetol. 2003; 2: 16.
16. *Rupp H., Schulze W., Vetter R.* Dietary medium-chain triglycerides can prevent changes in myosin and SR due to CPT-1 inhibition by etomoxir. Am. J. Physiol. Regul. Integr. Comp. Physiol. 1995; 269: R630-R640.
17. *Rupp H., Vetter R.* Sarcoplasmic reticulum function and carnitine palmitoyltransferase-1 inhibition during progression of heart failure. Br. J. Pharmacol. 2000; 131: 1748-1756.
18. *Stanley W.C., Chandler M.P.* Energy metabolism in the normal and failing heart: potential for therapeutic interventions. Heart Fail. Rev. 2002; 7: 115-130.
19. *Taylor M., Wallhaus T.R., DeGrado T.R., et al.* An evaluation of myocardial fatty acid and glucose uptake using PET with [18F] fluoro-6-thia-heptadecanoic acid [F]FDG in pateints with congestive heart failure. J. Nucl. Med. 2001; 42: 55-62.
20. *Wallhaus T.R., Taylor M., DeGrado T.R., et al.* Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. Circulation 2001; 103: 2441-2446.
21. *Yazaki Y., Isobe M., Takahashi W., et al.* Assessment of myocardial fatty acid metabolic abnormalities in patients with idiopathic dilated cardiomyopathy using 123I BMIPP SPECT: correlation with clinicopathological findings and clinical course. Heart 1999; 81: 153-159.