

THE EUROPEAN CARDIOLOGIST - JOURNAL BY FAX

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RECENT ADVANCES IN THE TREATMENT OF DILATED CARDIOMYOPATHY IN DIABETIC PATIENTS: THE ROLE OF 3-KAT INHIBITORS

Dilated cardiomyopathy and diabetes share several pathophysiological factors. Both conditions are characterized by abnormalities regarding micro- and macrovessels, sympathetic-vagal balance (autonomic neuropathy), collagen and contractile proteins, and cellular metabolism. In both dilated cardiomyopathy and diabetes, these pathogenetic factors are viciously interrelated and potentiate each other. Medical therapy of dilated cardiomyopathy is at present based on evidence that angiotensin-converting enzyme (ACE) inhibitors, β -blockers, and antialdosterone diuretics prolong survival and improve quality of life. These drugs, apart from their main mechanism of action, may also indirectly improve myocardial metabolism. However, specific medical interventions aimed at improving myocardial metabolism in dilated cardiomyopathy and diabetes have not been attempted until now. In this article, the potential importance of such an approach will be reviewed.

Metabolic alterations in heart failure and diabetes

Wasting of subcutaneous fat and skeletal muscle is relatively common in heart failure and diabetes, and suggests an increased utilization of noncarbohydrate substrates for energy production. In fact, fasting blood ketone bodies as well as fat oxidation during exercise have been shown to be increased in patients with diabetes as well as in those with heart failure.¹ Insulin resistance has been found to be associated with heart failure²; the consequent impaired suppression of lipolysis could lead to the development of ketosis. It is likely that metabolic alterations are aggravated when the two conditions, heart failure and diabetes, coexist. Experimental studies have shown that sodium dichloroacetate stimulates pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase.³ Stimulation of pyruvate dehydrogenase activity leads to enhanced glycolysis and utilization of lactate by the myocardium for aerobic respiration. Myocardial consumption of free fatty acids (FFA) is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly nonesterified FFA to glucose and lactate, finally resulting in improved left ventricular mechanical efficiency.⁴

A number of different approaches to manipulate energy metabolism in the heart are available. One way to increase glucose oxidation and decrease fatty acid metabolism in the heart is to decrease circulating fatty acid levels by the administration of glucose-insulin solutions, nicotinic acid, and β -adrenergic-blocking drugs. Another approach consists in directly modifying substrate utilization by the heart.

Effects of 3KAT inhibitors on left ventricular function and glucose metabolism

A recent study presented at the annual sessions of the American Heart Association held in Los Angeles, November 11 to 14, 2001, assessed whether the addition of the FFA inhibitor trimetazidine (TMZ) to standard current treatment of diabetic patients with ischemic dilated cardiomyopathy could effectively improve symptoms, exercise tolerance, left ventricular function, and glucose metabolism. Thirteen such patients on conventional therapy were randomly allocated in a double-blind fashion to either placebo or TMZ (20 mg tid), each arm lasting 15 days, and then again to placebo or TMZ for two additional 6-month periods. At the end of each period, all patients underwent a hyperinsulinemic/euglycemic clamp, two-dimensional echocardiography and exercise testing. M value (index of total body glucose disposal), basal and end-clamp forearm glucose uptake (FGU), New York Heart Association (NYHA) functional class, ejection fraction (EF), fractional shortening (FS), maximal rate-pressure product (RPP), and exercise time (ET) were evaluated. In the short term, compared with

placebo, M value (4.01 ± 1.82 versus 3.26 ± 1.56 , $P < 0.05$), EF ($46 \pm 6\%$ versus $40 \pm 8\%$, $P < 0.05$), FS ($23 \pm 5\%$ versus $20 \pm 5\%$, $P < 0.05$), RPP ($23\ 350 \pm 8366$ mm Hg \times beats per minute versus $21\ 022 \pm 7539$ mm Hg \times beats per minute, $P < 0.05$), and exercise time (411 ± 129 s versus 397 ± 143 s, $P = 0.36$) increased, while 8 patients had a 1-point decrease in NYHA class during TMZ. In the long term, TMZ maintained LV function and glucose metabolism improvement, while on placebo no changes were observed. Finally, long-term TMZ decreased by 1 point of the NYHA class in 7 patients, while on placebo 3 patients increased by 1 class and none improved. Therefore, short- and long-term TMZ improved left ventricular function, symptoms, and glucose metabolism in patients with diabetes and dilated ischemic cardiomyopathy. The observed short-term benefit from TMZ was maintained in the long term and contrasts with the natural history of the disease, as shown by the mild but consistent decrease in EF with placebo.⁵

The novel observation that TMZ could also improve overall glucose metabolism indicates an interesting ancillary property of the drug. In this study, in order to maximize the potential beneficial effects of TMZ on the overall utilization of glucose, only diabetic patients were recruited. Indeed, the known insulin-resistant state in patients with heart failure is certainly aggravated in those patients with overt diabetes. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose is grossly reduced. Since a major factor in the development and progression of heart failure is already a reduced availability of ATP, determining a metabolic state that has been defined as "energy starvation",⁶ glucose metabolism alterations, as present in overt diabetes, could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, TMZ stimulates total glucose utilization, including both glycolysis and glucose oxidation. Additionally, TMZ increases the incorporation of long-chain fatty acids into the cardiomyocyte membrane,⁷ thus significantly reducing the availability of cytosolic FFA and acylcarnitine, which can have deleterious effects on calcium handling. These effects are probably operative on both cardiac and skeletal muscle and therefore the effects of TMZ on glucose metabolism could be dependent on (1) improved cardiac efficiency and a consequent improvement of peripheral blood flow; and (2) improved peripheral glucose extraction and utilization.

In conclusion, the results of recent research support the concept that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by trimetazidine, a ketoacyl-coenzyme A thiolase (3-KAT) inhibitor, is an effective

In the event of any questions, or if you wish to receive the referenced publications, please contact fax n° 1 (246) 429 - 5848

HYPERTENSION	COVERSYL[®] 4mg	HEART FAILURE
	PERINDOPRIL	1 tablet daily
<p>Coversyl is a long-acting ACE inhibitor. International nonproprietary name: Perindopril. Indications: Essential hypertension. Congestive heart failure (adjunctive therapy). Dosage and administration: Hypertension: 4 mg once a day in the morning. If necessary, the dose may be increased to 8mg after one month of treatment. Coversyl should be taken before food. Congestive heart failure: Coversyl should be started under close medical supervision at a starting dose of 2 mg in the morning. This may be increased to 4 mg once blood pressure acceptability has been demonstrated. Elderly patients: start treatment at 2 mg daily. Contraindications: Children. Pregnancy. Lactation. Patients with a history of hypersensitivity to Coversyl. Precautions: Assess renal function before and during treatment where appropriate. Renovascular hypertension. Surgery/Anesthesia. Renal insufficiency: the dose should be cautiously adjusted in accordance with the creatinine clearance (refer to complete data sheet). Symptomatic hypotension is rarely seen, but is more likely in volume-depleted patients, those receiving diuretics, or with the first two doses. In diuretic-treated patients, stop the diuretic 3 days before starting Coversyl. A diuretic may later be given in combination if necessary; potassium-sparing diuretics are not recommended. Combination with neuroleptics or imipramine-type drugs may increase the hypotensive effect. Serum lithium concentrations may rise during lithium therapy. Side effects: Rare and mild, usually at the start of treatment. Cough, fatigue, asthenia, headache, disturbances of mood and/or sleep have been reported. Less often, taste impairment, epigastric discomfort, nausea, abdominal pain, and rash. Reversible increases in blood urea and creatinine may be observed. Proteinuria has occurred in some patients. Rarely, angioneurotic edema and decreases in hemoglobin, red cells, and platelets have been reported. Composition: Each tablet contains 4 mg of the tert-butylamine salt of perindopril. Presentation: Packs of 30 tablets of Coversyl 4mg (scored). Refer to data sheet for complete prescribing information</p> <p>Les Laboratoires Servier, 45520 Gidy, France. Correspondent: Servier International, 6, place des Pliades, 92415 Courbevoie cedex - France.</p>		

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adjunctive treatment in diabetic patients with postischemic cardiomyopathy, in terms of LV function improvement and glucose metabolism. Although highly suggestive, whether these benefits translate into improved survival needs to be ascertained by a multicenter trial. O

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