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NEW THERAPEUTIC STRATEGIES IN HEART FAILURE: TARGETING FREE FATTY OXIDATION

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Abstract

The possibility to modify cardiac metabolism by switching the fuel used by the myocardium could become increasingly important. Inhibitors of free fatty acids (FFA) oxidation could have an important role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from FFA metabolism and toward glucose metabolism may be an effective adjunctive treatment in terms of myocardial metabolism and left ventricular function improvement. These effects seem operative in heart failure syndromes regardless of their etiopathogenetic cause and not confined to those of ischemic origin.

Additionally, abnormalities of glucose homeostasis are consistently present in patients with heart failure, definitely contributing to the progression of the primary disease. If not adequately treated, in most patients glucose metabolism abnormalities will heavily contribute to the occurrence of complications, of which severe left ventricular dysfunction is one of the most frequent and insidious at present. Apart from a meticulous metabolic control of frank diabetes, special attention should be also paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The observed combined beneficial effects of FFA inhibitors on left ventricular function and glucose metabolism represent an additional advantage of these drugs, especially when myocardial and glucose metabolism abnormalities coexist.

In this paper, the recent literature on the beneficial therapeutic effects of FFA oxidation inhibitors on left ventricular dysfunction and glucose metabolism is reviewed and discussed.

Keywords: free fatty acids inhibitors, heart failure, left ventricular function, myocardial metabolism.

Introduction

Several aspects of myocardial metabolism of the failing heart resemble that of the diabetic heart. Fasting blood ketone bodies [*Lommi J. et al., 1996*] as well as fat oxidation during exercise [*Riley M. et al., 1993*] have been shown to increase in patients with heart failure. Insulin resistance has been found to be associated with heart failure [*Paolisso G. et al., 1991*] and the consequent impaired suppression of lipolysis could determine the development of ketosis. A number of different approaches have been used to manipulate energy metabolism in the heart. These involve both indirect measures, as well as the use of agents, which directly act on the heart to shift energy substrates utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of adenosintriphosphate (ATP) production per mole of oxygen utilized. Recent studies have outlined the potential benefits of these agents on regional and global myocardial dysfunction. These beneficial effects can be explained by the fact that by increasing utilization

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of glucose and lactate, which are more efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium can be improved by 16% to 26% [*Lopaschuck G.D., Stanley W.C., 1997*]. Additionally, heart and arm skeletal muscle glucose uptakes are inversely related to serum free fatty acid (FFA) levels [*Nuutila P., et al., 1994*] and increased FFA flux from adipose tissue to non-adipose tissue amplifies metabolic derangements that are characteristic of the insulin resistance syndrome [*Lewis G.F. et al., 2002*]. New findings also suggest that raised FFA levels not only impair glucose uptake in heart and skeletal muscle but also cause alterations in the metabolism of vascular endothelium leading to premature cardiovascular disease [*Steinberg H.O., Baron A.D., 2002*]. Therefore, FFA inhibitors could also play a beneficial role in terms of glucose metabolism homeostasis.

The aim of this paper is to review and summarize reported evidence on protective FFA inhibitors on left ventricular function and glucose metabolism, and their potential clinical application in heart failure patients.

Effects of metabolic modulation with 3-KAT inhibitors on left ventricular dysfunction. Agents that directly inhibit fatty acid oxidation include inhibitors of 3-ketoacyl coenzyme A thiolase (3-KAT), the last enzyme involved in ß-oxidation [*Kantor P.F. et al., 2000*]. They have been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from FFA to glucose oxidation [*Fantini E. et al., 1994*]. The experimental evidence indicates that this effect is predominantly caused by a selective block of long chain 3-KAT [*Kantor P.F. et al., 2000*]; however, this issue is still under debate [*Lopaschuk G.D. et al., 2003; MacInness A, et al., 2003*]. Based on the hypothesis that FFA inhibitors could act as metabolic modulators in the protection of ischemic myocardium, L. Brottier and colleagues assessed the value of long-term treatment with trimetazidine (TMZ), a 3-KAT inhibitor in patients with severe ischemic cardiomyopathy, who were already receiving conventional therapy [*Brottier L. et al., 1990*]. Twenty patients were randomized to either placebo or TMZ. All patients on TMZ, at 6 months follow-up, reported a clinically considerable improvement in symptoms and showed a higher ejection fraction compared to patients on placebo. The authors concluded their study recommending the use of TMZ as a complementary therapeutic tool in patients with severe ischemic cardiomyopathy.

On this basis, the effects of TMZ on dobutamine-induced left ventricular dysfunction in patients with angiographically proven coronary artery disease were assessed [*Lu C. et al., 1998*]. Patients were blindly and randomly assigned to a 15-day treatment period with either placebo or TMZ. They were then crossed over to the other regimen for another 15 days. At the end of each treatment period, a stress echo with dobutamine was performed. Both in resting condition and at peak dobutamine infusion, wall motion score index was significantly lower on TMZ therapy than on placebo. Furthermore, TMZ induced an increase in dobutamine infusion time and an increase of the administered dobutamine dose to the development of ischemia. These results indicated that TMZ may not only protect from dobutamine-induced ischemic dysfunction, but could also improve resting regional left ventricular function, as shown by the significantly decreased peak and resting wall motion score index during the active treatment period. A subsequent study confirmed these preliminary results [*Belardinelli R., Purcaro A., 2001*].

Modulation of myocardial metabolism by 3-KAT inhibitors in post-ischemic heart failure. Keeping in mind the concept that TMZ should, therefore, be able to promote the utilization of glucose and non fatty substrates by the mitochondria, attention was focused on heart failure, for which maintainance of metabolic efficiency is a crucial issue.

The effects of the addition of TMZ to standard treatment of diabetic patients with ischemic dilated cardiomyopathy on symptoms, exercise tolerance and left ventricular function, were assessed [*Fragasso G. et al., 2003*]. Thirteen such patients on conventional therapy were ran-

domly allocated in a double blind fashion to either placebo or TMZ, each arm lasting 15 days, and then again with placebo or TMZ for 2 additional 6 month periods. Both in the short and long terms, TMZ showed a significant beneficial effect on left ventricular function and control of symptoms, compared to placebo. The observed short-term TMZ benefit was maintained in the long-term and contrasts with the natural history of the disease, as shown by the mild but consistent decrease of EF when on placebo (Figure 1). These results paved the way to additional studies that have invariably confirmed the positive effects of TMZ in patients with post-ischemic left ventricular dysfunction [*Rosano G.M.C. et al., 2003; Vitale C. et al., 2004; Di Napoli P. et al., 2005*].

Modulation of myocardial metabolism by 3-KAT inhibitors in heart failure of different etiologies. The beneficial effect of TMZ on left ventricular function has been attributed to preservation of phosphocreatine (PCr) and ATP intracellular levels [*Lavanchy N. et al., 1987*]. Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [*Conway M.A. et al., 1991*]. The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on imbalance of myocardial oxygen supply and demand [*Yabe T. et al., 1995]*, and reduction of the total creatine pool, a phenomenon known to occur in heart failure [*Nascimben L. et al., 1996*]. In a recent study performed in patients with heart failure of different ethiologies on full standard medical therapy, it has been observed that the TMZ-induced improvement of functional class and left ventricular function is associated to an improvement of PCr/ATP ratio, supporting the hypothesis that TMZ probably preserves myocardial high energy phosphate intracellular levels [*Fragasso G. et al., 2006 a*]. These results appear particularly interesting, especially in view of previous evidence indicating the PCr/ATP ratio as a significant predictor of mortality [Neubauer S. et al., 1997].

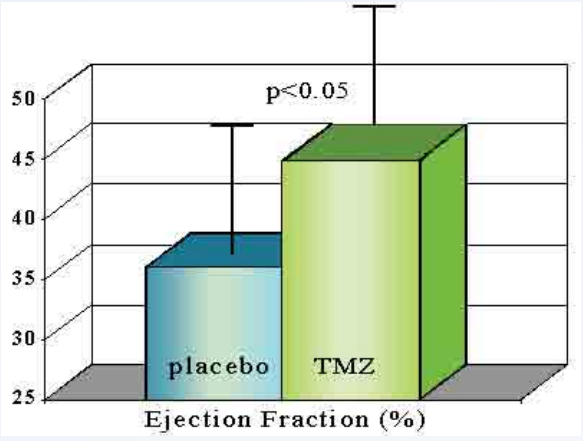

Figure 1. *Effects of trimetazidine and placebo on ejection fraction in diabetic patients with post-ischemic cardiomyopathy.*

Based on the results of this pilot study, it has also been tested whether TMZ added to usual treatment could also be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of different etiologies [*Fragasso G. et al., 2006 b*]. Compared to patients on conventional therapy alone, those on TMZ improved functional class, exercise tolerance, quality of life, and left ventricular function, and used less diuretics and less digoxin. Plasma B-type natriuretic peptide (BNP) level was also significantly reduced in patients on TMZ, compared to conventional therapy alone.

Similarly to TMZ, ranolazine has been also shown to significantly improve left ventricular performance in experimental models of heart failure [*Hayashida W. et al., 1994; Aaker A. et al., 1996; McCormack J.G. et al., 1996; Sabbah N.H. et al., 2002; Chandler M.P. et al., 2002*]. N. Sabbah and co-authors measured hemodynamics before and 40 minutes after intravenous ranolazine in a canine model of heart failure [*Sabbah N.H. et al., 2002*]. Results in 13 experimental dogs were compared with those obtained in 8 normal healthy dogs. Ranolazine significantly decreased left ventricular end-diastolic pressure and increased left ventricular ejection fraction in the absence of any effects on heart rate or blood pressure. In subsequent experiments from the same laboratory, Chandler et al. reproduced these findings and determined that the improvement in left ventricular performance was not associated with an increase in myocardial

oxygen consumption (MO_2) compared with an intravenous infusion of dobutamine that improved left ventricular performance to a similar extent, but was associated with a significant increase in MO_2 requirements [*Chandler M.P. et al., 2002*].

In a study of 15 patients with prior myocardial infarction and significantly reduced left ventricular function who received an intravenous ranolazine infusion, regional function was assessed in ischemic, infarcted, and normal left ventricular segments [*Hayashida W. et al., 1994*]. Global left ventricular function was not changed significantly after ranolazine infusion. However, ranolazine was associated with a significant increase in peak filling rate and regional wall lengthening during the isovolumic relaxation phase in ischemic left ventricular segments, suggesting evidence of improved regional diastolic function.

Finally, a recent study has evidenced that energy deficiency in heart failure might result from increased uncoupling proteins (i.e., less efficient ATP synthesis) and depleted glucose transporter protein (i.e., reduced glucose uptake) [*Murray A.J. et al., 2004*]. On this grounds, the adoption of drug therapies such as 3-KAT inhibitors, aimed at interrupting the metabolic vicious circle in heart failure, has been advocated [*Opie L.H., 2004*].

Overall, this data confirm that selective inhibition of 3-KAT represents a new therapeutic window in the treatment of patients with heart failure of different etiologies, and not only secondary to ischemic heart disease. A recent statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology has indicated partial fatty acid oxidation inhibitors, such as perhexiline and TMZ, as potential new tools in the treatment of advanced heart failure [*Metra M. et al., 2007*]. The time has come to test this therapeutical approach in a multicenter, randomized trial in patients with heart failure.

Modulation of glucose metabolism by 3-KAT inhibitors. Regulation of glucose metabolism is an important target in the control of cardiovascular risk factors. Abnormalities of glucose homeostasis range from frank diabetes to a state of insulin resistance, a definition used to indicate the necessity to increase insulin levels in order to maintain normal glycemic levels. Recent studies have identified a direct relation between endothelial dysfunction and insulin resistance [*Piatti P.M. et al., 2000a*]. Endothelin-1 levels have been shown to significantly correlate with fasting insulin levels, systolic and diastolic blood pressure, visceral obesity and triglyceride levels, confirming a close relationship between insulin resistance and endothelial function [*Piatti P.M. et al., 2000b*]. When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles [*Crettaz M. et al., 1981*]. Different degrees of endothelial dysfunction associated to a state of insulin resistance have been evidenced in most cardiovascular diseases such as hypertension [*Natali A. et al., 1997*], coronary artery disease [*Despres J.P. et al., 1996; Yoshimura T. et al., 2003*], microvascular angina [*Piatti P.M. et al., 1999*] and heart failure [*Paolisso G. et al., 1991*]. On the other hand, insulin resistance is a pathological condition that is rarely diagnosed as a distinct entity. In a recent study, our group has shown that more than 50% of patients submitted to coronary stenting for ischemic heart disease and with normal baseline blood glucose levels present abnormal hyperglicemia after an oral glucose tolerance test [*Piatti P.M. et al., 2003*]. These abnormalities are associated to a higher probability of restenosis [*Piatti P.M. et al., 2003*]. These results are supported by previous studies showing that impaired glucose tolerance not only runs the risk of developing overt diabetes and its associated microvascular complications but also has an increased risk of cardiovascular morbidity and mortality compared with healthy glucose-tolerant patients [*The Decode Study Group, 1999*]. Therefore, early detection of impaired glucose tolerance would permit initiation of secondary preventive treatment measures in such patients.

Effects of FFA inhibition on glucose metabolism. Lowering raised plasma triglycerides and FFA levels could be the first therapeutic option to decrease the heart's reliance on fatty acids and overcome the fatty acid inhibition of myocardial

glucose utilization. Indeed beta-blockers, by reducing peripheral lypolysis, should reduce FFA availability. Interestingly enough, a recent study has shown that one of the main effects of the beta-blocker carvedilol is the reduction of FFA utilization in favor of greater glucose utilization in patients with stable NYHA functional class III heart failure [*Wallhaus T.R., et al., 2001*]. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with ß-adrenoreceptor blockade in the treatment of heart failure. Nevertheless, only non-selective, compared to selective ß-adrenoreceptor blockers, appears to shift total body substrate utilization from lipid to glucose oxidation [*Podbregar M., Voga G. , 2002*], and this could be one of the reasons of better survival rates observed with the formers [*Poole-Wilson P.A. et al., 2003*]. Additionally, central inhibition of sympathetic nervous activity with moxonidine in heart failure has been associated with increased mortality [*Cohn J.N. et al., 2003*]. In fact, despite a significant reduction of cathecolamine spillover, moxonidine has been shown to increase FFA utilization and increase myocardial oxygen consumption [*Mobini R. et al., 2006*]. This could be the reason for the failure of central sympathetic inhibition to prevent deaths in long-term studies in patients with heart failure and also indicates that the predominant mechanism of action of beta-blockers is probably related to their peripheral antilypolytic action.

Another possibility is to directly induce muscles to reduce FFA utilization in favor of glucose oxidation. The use of a partial fatty acid inhibitor could play a very specific role. In fact, as previously outlined, most cardiac diseases are associated to combined insulin resistance and endothelial dysfunction. Therefore, improving the cardiac metabolic milieu by partially inhibiting FFA utilization could be particularly effective.

Keeping in mind the concept that 3-KAT inhibitors should, therefore, be able to promote the utilization of glucose and non fatty substrates by the mitochondria, attention has been focused on this specific issue. In fact, apart from improving left ventricular function in cardiac patients, it has been recently shown that TMZ could also improve overall glucose metabolism in the same patients (Figures 2-3), indicating an attractive ancillary pharmacological property of this class of drugs [*Fragasso G. et al., 2003*]. In fact, the known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are significantly reduced. Indeed, since a major factor in the development and progression of heart failure is already a re-

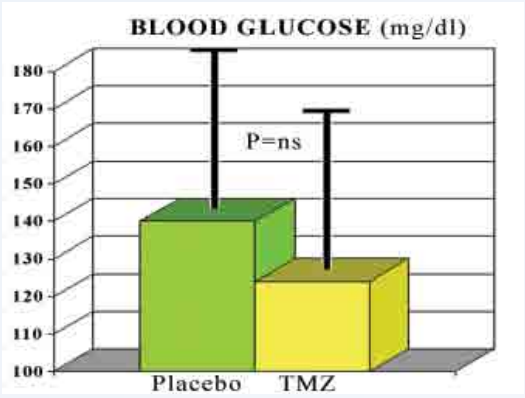

Figure 2. *Long-term effect of trimetazidine and placebo in diabetic patients with post-ischemic cardiomyopathy on blood glucose.*

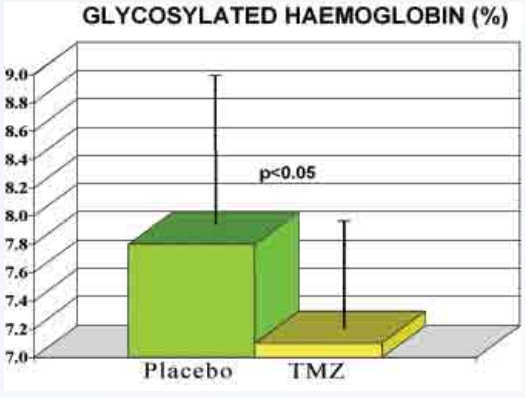

Figure 3. *Long-term effect of trimetazidine and placebo in diabetic patients with post-ischemic cardiomyopathy on glycosylated haemoglobin.*

duced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibition of fatty acid oxidation, TMZ stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of TMZ on glucose metabolism could therefore be dependent on a) improved cardiac efficiency; b) improved peripheral glucose extraction and utilization. Finally, considering the known relation between ET-1 concentration and glucose metabolism abnormalities [*Piatti P.M. et al., 2000 a*], the observed beneficial effects of TMZ on glucose metabolism could also be partly ascribed to the positive effect of the drug on ET-1 levels reduction.

Animal studies have also suggested that TMZ improves blood glucose utilization in rats with fasting hyperglycemia [*Cano C. et al., 2003*]. On this grounds, both forearm glucose and lipid metabolism and forearm release of endothelial vasodilator and vasoconstrictor factors have been evaluated during a prolonged inhibition of β-oxidation by TMZ in patients with post-ischemic left ventricular dysfunction. TMZ increased both insulin-induced forearm glucose oxidation and forearm cyclic-guanosine monophosphate release, while forearm ET-1 release was decreased [*Monti L.D. et al., 2006*]. Although these findings need further confirmation, the effects of TMZ at the skeletal muscle level add a new therapeutic window in the treatment of patients with ischemic heart disease and type 2 diabetes.

Based on these data, the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) has included metabolic agents such as TMZ, as potential medical aids in the treatment of cardiac patients with diabetes [*Ryden L. et al., 2007*].

Effects of 3-KAT inhibitors on endothelial function. It has been recently observed that TMZ could reduce endothelin release in cardiac patients [*Fragasso G. et al., 2002; Fragasso G. et al., 2003; Monti L.D. et al., 2006*] (Figure 4). Growth factors, vasoactive substances and mechanical stress are involved in the endothelin-1 (ET-1) increase in heart failure patients. Despite the known adaptative aspect of supporting contractility of the failing heart, persistent increases in cardiac ET-1 expression in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [*Yamauchi-Kohno R. et al., 1999*].

TMZ-induced reduction of intracellular acidosis in ischemic myocardium could not only influence myocardial but also endothelial membranes [*Maridonneau-Parini I, Harpey C., 1985*]. By decreasing endothelial damage, TMZ could inhibit ET-1 release that, in turn, will finally decrease myocardial damage. A second hypothesis is that, decreasing the effects of chronic myocardial ischemia, TMZ could inhibit ET-1 release. Therefore, the observed decrease in ET-1 release with TMZ, could likely be linked to TMZ-induced reduction of myocardial ischemia. Finally, keeping in mind the close relation between endothelium and insulin sensitivity, the observed effects of TMZ on endothelial function could also explain the beneficial action of TMZ on glucose metabolism.

Similarly, ranolazine has also been shown to exert beneficial effects on glucose metabolism. The anti-anginal efficacy and safety of ranolazine in diabetic and non-diabetic patients included in the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial [*Chaitman B.R. et al.,*

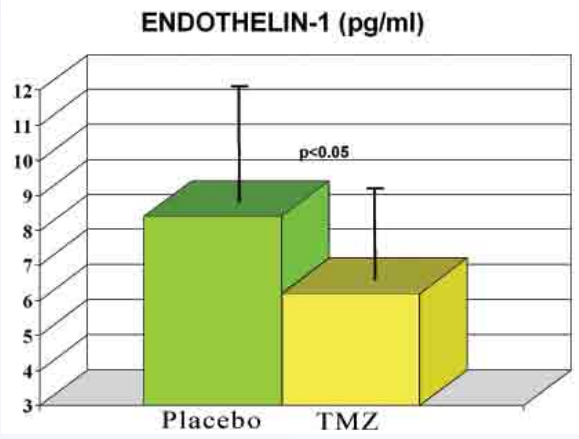

Figure 4. *Long-term effect of trimetazidine and placebo in diabetic patients with post-ischemic cardiomyopathy on endothelin-1*

2004] were studied. Glycaemic control was also assessed in CARISA and its long-term open-label extension study. The anti-anginal efficacy and safety of ranolazine for angina were similar between diabetic and non-diabetic patients. Additionally, ranolazine significantly improved glycaemic control in diabetic patients [*Timmis A.D. et al., 2006*] confirming that, apart from their primary cardiac action, this class of drugs yields also this important ancillary effect on glucose metabolism.

Other inhibitors of fatty acids oxidation. Etomoxir, perhexiline and oxfenicine are carnitine palmitoyl transferase I (CPT-I) inhibitors. CPT-I is the key enzyme for mitochondrial FFA uptake; its inhibition, therefore, reduces FFA oxidation and their inhibitory effect on pyruvate dehydrogenase. As a consequence, glucose oxidation is increased [*Lopashuk G.D. et al., 1988; Ratheiser K. et al., 1991*]. Etomoxir, initially developed as an anti-diabetic agent, has then been observed to improve left ventricular performance of pressure-overloaded rat heart [*Turcani M., Rupp H., 1997*]. These effects have been considered due to a selective modification of gene expression of hypertrophic cardiomyocytes [*Zarain-Herzberg A., Rupp H., 2002*]. Etomoxir could also increase phosphatase activation, have a direct effect on peroxisome proliferator activated receptor-alpha and up-regulate the expression of various enzymes involved in beta-oxidation [*Zarain-Herzberg A., Rupp H., 2002*]. The first clinical trial employing etomoxir in heart failure patients has shown a significant clinical and cardiac function improvement [*Schmidt-Schweda S., Holubarsch C., 2000*]. In experimental animal studies, etomoxir has also been shown to improve glucose metabolism [*Schmitz F.J. et al., 1995*]. However, the use of etomoxir may be limited by the the observation that it may cause cardiac hypertrophy [*Caberos A. et al., 2003*] and oxidative stress [*Merril C.L. et al., 2002*].

Analogously to etomoxir, oxfenicine and perhexiline, originally classified as calcium antagonists, reduce cardiac utilization of long chain fatty acids by inhibiting CPT-I [*Stephens T.W. et al., 1985; Jeffrey F.M. et al., 1995; Kennedy J.A. et al., 2000*]. They have been initially developed as antianginal agents [Bergman G. et al., 1980; Cole P.L. et al., 1990]. However, they have been recently employed in patients with heart failure. In a recent study, metabolic modulation with perhexiline improved O2 max, left ventricular ejection fraction, symptoms, resting and peak stress myocardial function, and skeletal muscle energetics [Lee L. et al., 2005]. Therefore, similarly to 3-KAT inhibitors, CPT-I inhibitors may represent a novel treatment in patients with heart failure with a good safety profile, provided that the dosage is adjusted according to plasma levels. In fact, perhexiline should be used with caution because of reported hepatotoxicity and peripheral neuropathy [Meier C. et al., 1986; Killalea S.M., Krum H., 2001].

Additional applications of FFA inhibition. Clinical studies have shown that partial FFA inhibition may exert cardioprotective effects in the setting of myocardial ischaemia including acute myocardial infarction [*Steg P.G. et al., 2001; Padadopoulos C.L., et al., 1996; Di Pasquale P. et al., 1999*]. In patients undergoing cardiac surgery, J.N. Fabiani et al. demonstrated that TMZ may reduce ischaemia-reperfusion damage during cardiac surgery and that pretreatment with TMZ allows the patient to face the operation with better ventricular function [*Fabiani J.N. et al., 1992*]. G. Kober et al. have demonstrated that TMZ reduces pre-procedural myocardial cell ischaemia as assessed by the duration and amplitude of ST elevation during percutaneous coronary interventions [*Kober G. et al., 1992*]; however, whether its cytoprotective effects could translate into a reduction of myocardial necrosis is unknown. A recent study has indeed shown that pretreatment with a 60 mg acute oral loading dose of TMZ before elective percutaneous coronary interventions limits myocardial damage, as shown by a lower total amount of cardiac troponin I release after coronary angioplasty [*Bonello L. et al., 2007*]. TMZ is also beneficial in preventing ischaemia-reperfusion injury. In fact, a recent animal experiment demonstrated that TMZ could limit lethal ischaemia-reperfusion injury by inhi-

biting mitochondrial permeability transition pore opening, which represents a crucial event in cardiomyocyte death following myocardial ischaemia-reperfusion [*Weiss J.N. et al., 2003; Argaud L.et al., 2005*]. Altogether, these effects could explain the reduction of cardiac myonecrosis in patients pretreated with TMZ before cardiac surgery or angioplasty. The question of whether the observed beneficial effects of TMZ could translate into an improved post-procedural outcome needs further investigation. Clearly, these results warrant large-scale longitudinal studies to investigate the effects of pre-procedural oral TMZ treatment on late outcome in patients undergoing elective myocardial revascularization.

Conclusions

Inhibitors of fatty acids oxidation could have an important role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism may be an effective adjunctive treatment in patients with heart failure, in terms of left ventricular metabolism and function improvement. These effects seem operative in heart failure syndromes regardless of their etiopathogenetic cause and not confined to those of ischemic origin.

Additionally, most cardiac diseases are associated to abnormalities of glucose homeostasis, which definitely contribute to the progression of the primary disease. If not adequately treated, in most cardiac patients glucose metabolism abnormalities will heavily contribute to the occurrence of complications, of which severe left ventricular dysfunction is one of the most frequent and insidious at present. Apart from a meticulous metabolic control of manifested diabetes, special attention should be also paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The observed combined beneficial effects of 3-KAT inhibitors on left ventricular function and glucose metabolism represent an additional advantage of these drugs, especially in those cardiac patients in whom myocardial and glucose metabolism abnormalities coexist.

Although highly suggestive, whether these benefits would translate into improved survival should be ascertained by a multicenter trial.

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