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Editorial

Metabolic therapy for heart failure

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This editorial refers to "Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease" † by C. Vitale et al. on page 1814

The concept that high blood free fatty acids (FFA) can be damaging to the ischaemic myocardium, especially in the presence of raised circulating catecholamines, is well entrenched.[1] Furthermore, when the myocardial metabolism of FFA is limited and that of glucose enhanced by a variety of procedures, such as decreasing blood levels of FFA by insulin and/or glucose, or by anti-adrenergic therapy, or by inhibitors of the entry of activated fatty acids into the mitochondria, or by partial inhibitors of fatty acid oxidation by agents such as trimetazidine (TMZ) or ranolazine, markers of ischaemia generally improve. Clinical applications of these ideas include the use of glucose–insulin–potassium (GIK) or glucagon-like peptide for acute myocardial infarction and TMZ or ranolazine as anti-anginal agents. What is less well known is that similar concepts can be applied to heart failure, a hyperadrenergic state in which circulating FFA are also increased.[2] Logically, such drugs should also work against heart failure, especially when there is an ischaemic basis. In this issue of the *Journal*, an important article by Vitale et al.,[3] describes the benefits of TMZ when given chronically to patients with this exact clinical profile. This editorial examines three possible mechanisms of this TMZ-induced benefit, with emphasis on the effects on mitochondria.

Indirectly increased glucose oxidation

An established site of action of TMZ is inhibition of mitochondrial fatty acid oxidation[4] which relieves fatty acid-induced inhibition of pyruvate dehydrogenase. The result is increased glucose oxidation and production of membrane-protective glycolytic ATP,[5] a potential source of energy for the sodium pump.[6] The end result of the improved substrate utilisation is enhanced cardiac mechanical function.[7]

Decreased fatty acid-induced oxygen wastage

One common concept is that drugs such as TMZ and ranolazine are oxygen-sparing by switching the metabolism from fatty acids to that of glucose. However, a complete switch from exclusive use of FFA as an energy source to glucose as the sole fuel can only save 11–13% of the myocardial oxygen use according to calculations based on the P/O ratio.[8] Yet such a complete metabolic switch could not be achieved by either TMZ or ranolazine which are partial and not total inhibitors of fatty acid oxidation. Strangely, considering the scientific importance of this mechanism, no one has performed the simple experiment of measuring the oxygen uptake of the normal beating heart (at various fatty acid concentrations) before and after TMZ or ranolazine. However, we do have data on the effect of abnormally high FFA levels on the oxygen uptake. Taking the physiological FFA level as between 0.4 and 0.6 mmol/l, a modest elevation to levels between 0.8 and 1.2 mmol/l increase the oxygen uptake of the isolated rat heart by about 33%,[9] while excessively high levels of greater than 3.0 mmol/l increases the oxygen uptake of the pig heart by 48% irrespective of the work load.[10] These data can be explained by the uncoupling effect of high circulating FFA levels.[2] Hypothetically, we propose that TMZ and ranolazine can lessen the uncoupled respiration found in heart failure, thereby explaining the large increase in myocardial mechanical efficiency.[7]

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Mitochondrial mechanisms and uncoupling proteins

As electrons are shuttled through complexes I—IV of the mitochondrial respiratory chain, protons are extruded into the inter-mitochondrial membrane space, resulting in a proton electrochemical potential gradient developing across the inner mitochondrial membrane (Fig. 1). The protons subsequently re-enter the mitochondrial matrix via the ATP synthase which drives the phosphorylation of ADP to ATP. Thus, electron transport is coupled to mitochondrial oxidative phosphorylation. However, mitochondria can have continued oxygen consumption in the absence of ADP, indicating that mitochondrial respiration is not always tightly coupled to oxidative phosphorylation. The outcome of such proton ''leaking'' is the dissipation of the proton gradient across the inner mitochondrial membrane, resulting in diminished mitochondrial ATP production (Fig. 1). Furthermore, mitochondrial uncoupling will result in oxygen ''wastage'' since more oxygen will be required to produce equivalent amounts of mitochondrial ATP. Uncoupling proteins (UCPs) may promote mitochondrial proton leakage.[11] Studies performed thus far have expanded the portfolio of functionality attributed to cardiac UCP2 and UCP3 from acting as classical uncouplers to include roles in antioxidant defence, nutritional partitioning, and the efficiency of energy production.[11] Fatty acids may play an important role in facilitating mitochondrial uncoupling via UCPs because elevated cardiac fatty acid

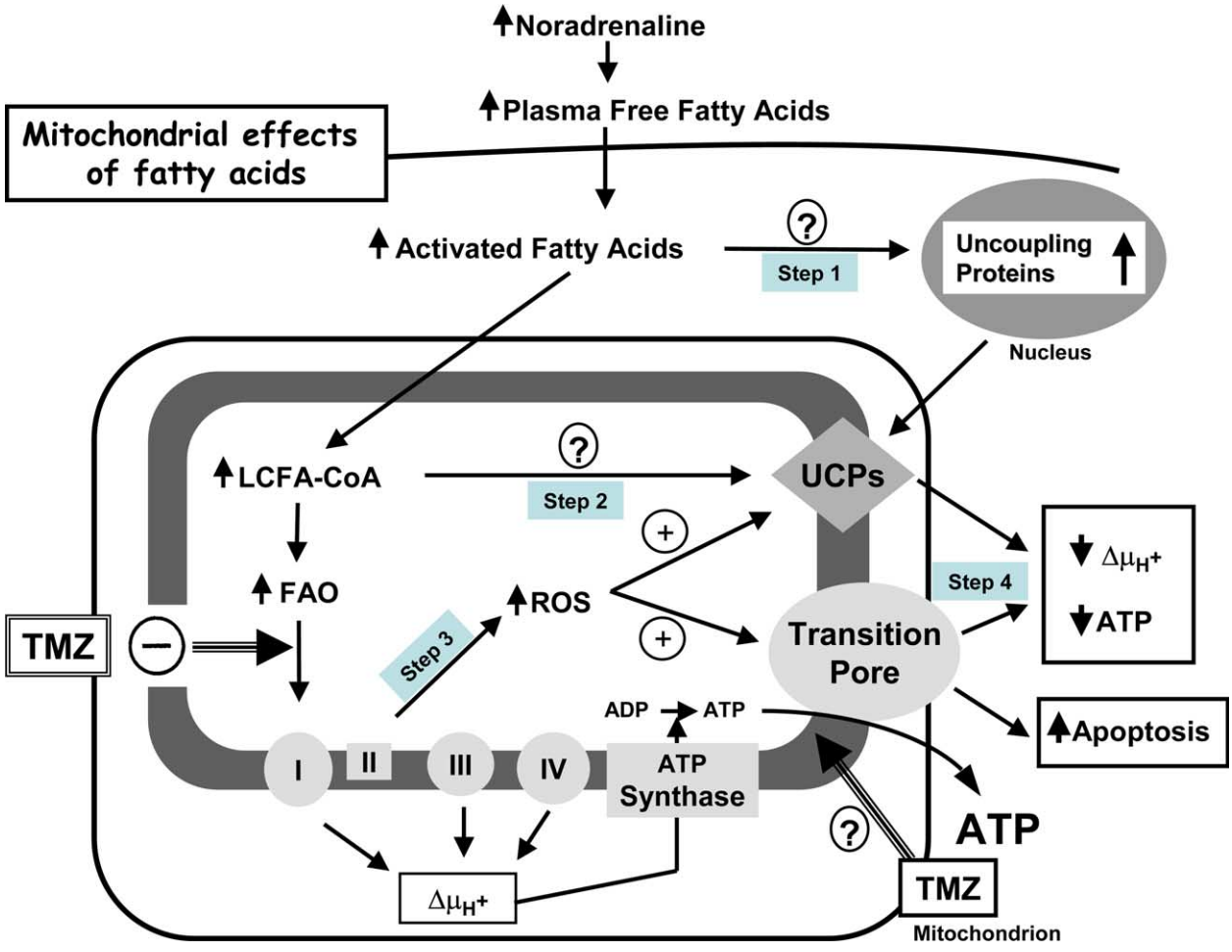

Fig. 1 During heart failure, elevated noradrenaline levels activate β-adrenergic pathways in adipocytes thereby increasing systemic free fatty acid levels. Fatty acids are activated inside the cardiomyocyte to form long-chain fatty acyl-CoAs (LCFA-CoA). LCFA-CoAs may induce gene expression of cardiac-enriched uncoupling proteins (UCP) in the nucleus (Step 1). Upon importation into the mitochondrial matrix, LCFA-CoAs may uncouple mitochondrial oxidative phosphorylation via UCPs (Step 2). LCFA-CoAs also enter the mitochondrial fatty acid β-oxidation (FAO) spiral. Reducing equivalents generated subsequently enter the mitochondrial respiratory chain complexes, resulting in the formation of a proton gradient $(\Delta\mu_H^+)$ across the inner mitochondrial membrane. Protons located within the intermitochondrial membrane space re-enter the mitochondrial matrix through ATP synthase, resulting in mitochondrial ATP synthesis. Mitochondrial ATP is exported to the cytosol by adenine nucleotide translocator, proposed to form part of the mitochondrial permeability transition pore. With increased β-adrenergic stimulation and mitochondrial FAO, levels of mitochondrial reactive oxygen species (ROS) may increase and activate UCPs and/or promote transition pore opening (Step 3). This in turn will result in proton ''leak'' and dissipation of the membrane potential, thereby diminishing mitochondrial ATP production (Step 4). Transition pore opening will also trigger programmed cell death (apoptosis) (Step 4). Chronic administration of TMZ may prevent such damaging mitochondrial effects by inhibiting cardiac mitochondrial FAO or by direct ''anti-uncoupling'' effects.

uptake and lipid oxidation rates are reported in patients with congestive heart failure.[12] Augmented fatty acid oxidation may result in a number of detrimental effects, including decreased efficiency of mitochondrial ATP production, increased apoptosis and eventually reduced contractile reserve. However, direct proof that TMZ decreases activation of myocardial uncoupling proteins via depressed fatty acid oxidation is still outstanding. Of interest, TMZ also has protective mitochondrial ''anti-uncoupling'' effects in fatty acid-free media.[13]

Fatty acid metabolism and impaired myocardial contractility

Besides these mitochondrial effects, increased fatty acid supply and utilisation by the failing heart may have a number of detrimental consequences that may contribute to impaired contractility. First, activated fatty acids act as ligands for the fatty acid-responsive transcriptional modulator, peroxisome proliferator-activated receptor-α (PPAR).[14] PPARα activation induces genes that encode enzymes of fatty acid utilisation, thereby increasing mitochondrial fatty acid oxidation capacity in the heart. Reactivation of PPARα in the hypertrophied rat heart provokes mechanical failure.[15] Also, PPARα helps to activate cardiac UCP gene expression (Step 1, Fig. 1).[11,16] Secondly, activated fatty acids may play an important role in mitochondrial uncoupling via UCPs (Step 2, Fig. 1) and/or by locking adenine nucleotide translocator (ANT) into a specific conformational structure that promotes opening of the mitochondrial permeability transition pore,[17] which in turn increases apoptosis.[18] Thirdly, elevated mitochondrial fatty acid oxidation increases production of mitochondrial reactive oxygen species by the mitochondrial respiratory chain. Reactive oxygen species activate UCPs and promote transition pore opening (Step 3, Fig. 1) that predisposes to increased apoptosis that could eventually compromise cardiac output (Step 4, Fig. 1).

Effects of trimetazidine in heart failure

The study by Vitale et al.,[3] demonstrates that chronic administration of TMZ, a specific partial inhibitor of fatty acid oxidation, to elderly patients with heart failure resulted in enhanced cardiac output and quality of life. The implications of chronic TMZ administration in terms of overall cardioprotective mechanisms are unclear. Potential chronic cardioprotective effects, besides the indirect increase in glucose metabolism,[4] may include diminished mitochondrial uncoupling, enhanced efficiency of mitochondrial ATP production and reduced apoptosis. In heart failure patients,[2] there is a positive correlation between increased plasma FFA levels and UCP2/UCP3 expression. These data are consistent with the notion that elevated noradrenaline levels during heart failure increase lipolysis and thus elevate plasma FFA levels. Speculatively, TMZ could diminish the FFA-induced uncoupling of respiration that we postulate occurs in heart failure, a mechanism which could explain the increased efficiency of cardiac contraction achieved by the closely related drug, ranolazine, in the failing dog heart.[7]

A new approach to the therapy of heart failure

Thus we have argued that heart failure is a hyperadrenergic state that increases circulating FFA levels to cause mitochondrial uncoupling and hence inefficiency of work. An indirect consequence is decreased myocardial utilisation of glucose and decreased protective glycolysis. Glucagon-like peptide is an insulin-like agent that promotes myocardial uptake of glucose, while increasing mechanical efficiency in dogs with pacing-induced heart failure.[19] All agents that decrease FFA levels or inhibit myocardial oxidation of FFA should also improve the work efficiency of the failing heart, as with TMZ or ranolazine, etomoxir[20] and the beta-blocker metoprolol.[21] The outstanding challenge is now to undertake a serious study of the effect of TMZ or ranolazine on human heart failure, including the non-ischaemic variety, making the study large enough to test the novel hypothesis that metabolic therapy by TMZ could reduce death rates in otherwise fully treated patients.

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