Can metabolic manipulation reverse myocardial dysfunction?

See page 2164, doi:10.1053/euhj.2001.2653 for the article to which this Editorial refers

The work by Bellardinelli et al. [1] joins a number of small but well documented studies which have shown improvement of cardiac function in ischaemic cardiomyopathy with the metabolically active drug trimetazidine [2,3]. This drug has already been shown to improve ischaemic changes in exercise testing in patients with chronic angina pectoris [4].

It can be postulated that trimetazidine acts on chronically hibernating myocardium by diminishing the effects of ischaemia and thus improving function in a way analogous to revascularization, i.e. by restoring energy/function imbalance. The improvement shown in the present study under basal conditions (a 19% increase in the ejection fraction) is not less than that seen in various revascularization studies [5].

Should this improvement be continued it could evolve into a major mainstay in the treatment of chronic congestive heart failure caused by ischaemic heart disease. It is estimated that 11% [6] to 33% [7] of patients considered candidates for heart transplantation could obtain a meaningful improvement in cardiac function by securing an increase in blood flow. In the present study many segments demonstrated a viable response with a concomitant diminution of the ischaemic biphasic response. As would be expected, the benefit of the drug was seen in initially hypokinetic segments. The akinetic segments did not improve. An improvement only in patients with viable and hibernating myocardium would explain this. However, the drug could arguably also be helpful in non-hibernating but ischaemic segments by improving energy conditions in the compensating, remote, overworked myocardium supplied by stenotic arteries. These eventualities should be differentiated in the future. Additionally, the drug may benefit patients either by obviating the need for revascularization, or by rendering more patients suitable for revascularization by increasing viable segments, as the authors point out.

Trimetazidine is not the only drug metabolically modifying ischaemia [8]. Three other drugs are also shown to share its action of shifting energy production from the fatty acids to glucose under ischaemic conditions, i.e. carnitine [9,10], ranolazine [9,11] and etomoxir [9]. All [9], like trimetazidine [12] have been shown to protect the isolated heart from various forms of ischaemic insults under a vast array of experimental conditions. Moreover, apart from acting on hibernation, this drug could be beneficial by attenuating stunning which commonly occurs after clinical instances of ischaemia [13]. Here, a note of caution should be sounded: experienced and very active researchers have shown that trimetazidine ‘inhibits’ preconditioning [12], another extremely beneficial and protective mechanism which the myocardium marshalls against ischaemia under both experimental and clinical conditions. If a drug, although acting anti-ischaemically were to negate this mechanism, it would be a hollow triumph, especially since preconditioning is repeatedly demonstrated as protecting against necrosis in everyday life [14].

This author hopes that additional studies will confirm another, more hopeful condition: that the apparent ‘inhibition’ of one protective mechanism by another is in fact a sharing by both of a significant but disparate antiischaemic mechanism, a mechanism whose additional benefit is masked under the experimental conditions currently employed. Minners et al. [15] postulate that the attenuation of preconditioning-like cardioprotection by trimelazidine may be explained by its limitation in preconditioning-induced mitochondrial swelling [16]; thus mitochondrial protection via trimelazidine can limit the cardioprotection of preconditioning. Probably and hopefully longer periods of ischaemia or different sequences of the metabolic insult might manifest a summation and not an inhibition of benefits.

One can envisage a comparison of the beneficial effects of beta-blockade, angiotensin inhibition either by ACE inhibitors or angiotensin receptor blockers and metabolic manipulation, as well as comparisons of combinations of the above medications. However,
another possibility should not be overlooked: etomoxir has already been assayed as an antifailure treatment in a small but careful trial[17]. In this study the population consisted mostly of idiopathic dilated cardiomyopathy patients. In this group etomoxir was postulated to exert its salutary effect by producing a shift of the isomyosin profile from V₃ to V₁. The latter isoform is more active and endows the myocyte with greater contractility, thus improving cardiac function[18]. However, this isoform shift may well not be a manipulation acting in isolation. Various conditions can cause a myosin shift from the fast adult to the slow fetal, i.e. pressure overload, diabetes mellitus, hypothyroidism. In most of these energy and cell integrity conservation, with resultant functional salvage, are the initiating mechanisms. In the diabetic heart failure model, increased reliance on fatty acid metabolism is very important[18]. By conserving energy under duress these drugs may afford to the myocyte extra fuel against ischaemia. In this context it should not be forgotten that ACE inhibition in the heart should undeniably inspire a host of metabolic weapons against ischaemia. But even under a less hopeful light they should open an era of metabolic interventions. Cardiovasc Res 1997; 33: 243–57.

I hope that the findings of Bellardinelli et al[1] will be substantiated and open an era of metabolic weapons against ischaemia. But even under a less hopeful light they should undoubtedly inspire a host of clinical and experimental investigations.

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References


