

EDITORIAL

Myocardial metabolic manipulation: a new therapeutic approach in heart failure?

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Myocardial metabolic manipulation using drugs such as trimetazidine may offer a new therapeutic approach to the treatment of heart failure

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MYOCARDIAL METABOLIC MANIPULATION

For many years there has also been interest in another approach to treating myocardial ischaemia in patients with heart failure. This approach involves metabolic manipulation of the myocardium.³ At least four agents may act in this way: etomoxir, perhexiline, ranolazine, and trimetazidine.³ None of these drugs is believed to have a significant inotropic, chronotropic, or vasodilator action at rest or during exercise, a very attractive feature for patients already taking multiple vasoactive medications.

What is the hypothesis behind myocardial metabolic manipulation? Under aerobic conditions, the human heart mainly uses free fatty acids (FFA) to generate energy (60–90% of the energy produced), with carbohydrate metabolism contributing only a small proportion (10–40%) of the adenosine triphosphate (ATP) generated. However, under hypoxic conditions—for example, during ischaemia—a shift towards glucose metabolism is desirable; although FFA metabolism yields more ATP per gram of substrate, it requires greater oxygen consumption. During ischaemia, FFA metabolism suppresses glucose oxidation, increases lactate and hydrogen ion production and, thus, leads to a fall in intracellular pH.³ This accelerates myocyte sodium and calcium overload, exacerbating the ischaemic insult and cardiac dysfunction. Moreover, ATP itself is also necessary to maintain cellular ionic homeostasis. Although glucose metabolism is increased during ischaemia, FFA metabolism is still predominant. Pharmacological interventions aimed at reducing FFA oxidation and increasing glucose metabolism may, therefore, be “cytoprotective” in myocardium subjected to repeated ischaemia. Similarly, there is also evidence that enhancement of carbohydrate oxidation in heart failure (as opposed to demand ischaemia) increases cardiac contractility and that reliance on FFA oxidation in heart failure may contribute to systolic dysfunction; put simply, the heart seems to pump more efficiently if the fuel is glucose. In other words, a shift from FFA oxidation to glucose oxidation may be good for both ischaemia and myocardial systolic dysfunction.

TRIMETAZIDINE

Trimetazidine is one of a number of drugs which may act in this way. Its molecular target,

Abbreviations: ACE, angiotensin converting enzyme; ATP, adenosine triphosphate; FFA, free fatty acids; NYHA, New York Heart Association

In most “developed” countries, coronary artery disease is now the most common cause of heart failure due to reduced left ventricular systolic function. Much, however, still needs to be understood about the relation between these two conditions. Myocardial infarction is a definite cause of ventricular damage and heart failure. Whether heart failure commonly occurs in patients with coronary artery disease, but without prior infarction, is much less clear. Similarly, there is not a consensus about the goals behind the treatment of coronary artery disease in patients with heart failure. Relief of angina is an obvious aim. Improving prognosis is another, though how this is achieved is less obvious, especially in patients without angina. There has also been much interest in the notion that, in these patients, ameliorating one or more of the various manifestations of myocardial ischaemia, assuming that they can be accurately measured, might improve ventricular function and thereby the symptoms of heart failure and prognosis.

There are many potential approaches to the treatment of myocardial ischaemia in patients with coronary artery disease, reduced left ventricular systolic function, and heart failure. Percutaneous or surgical “revascularisation” is indicated for relief of angina but may be risky. The value of “revascularisation” in patients without angina is unknown and two studies are currently underway to determine whether these interventions might improve prognosis.^{1,2}

Numerous conventional anti-ischaemic drug treatments are also available. One type, a β blocker, improves left ventricular function, the symptoms of heart failure, and clinical outcomes, but also has these benefits in patients with heart failure and no coronary disease. Others, such as nitrates, reduce ischaemia but do not improve systolic function or heart failure. There are also anti-ischaemic drugs which have detrimental effects in patients with heart failure, notably the calcium channel blockers, with the exception of amlodipine and, perhaps, felodipine. Lastly, some drugs, such as angiotensin converting enzyme (ACE) inhibitors and statins, have an anti-infarction effect (presumably protecting from further ventricular injury and failure), but do not relieve ischaemia.

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although still debated, is thought to be the last enzyme involved in mitochondrial fatty acid β -oxidation, long chain 3-ketoacyl coenzyme A thiolase.⁴ Whatever the precise molecular mechanism, the anti-ischaemic effect of trimetazidine is likely due to a metabolic shift, leading to increased glucose oxidation.

In this issue of *Heart*, Di Napoli and colleagues report an open label, single centre study examining the effect of trimetazidine in patients who, after angiography, were deemed not to be candidates for "revascularisation".⁵ We are not told, however, what proportion of patients had angina or what other evidence there was of ischaemia. Though most patients were treated with an inhibitor of the renin-angiotensin system, only about half were taking a β blocker. Treatment with trimetazidine, for 18 months, was associated with improvements in New York Heart Association (NYHA) functional class, left ventricular ejection fraction, and other indices of cardiac remodelling. In addition, plasma C reactive protein concentration increased over time in the control group but remained stable in the trimetazidine group.

What are we to make of these findings? The changes in remodelling are easiest to interpret as the echocardiographic analyses were blinded; however, the open label study design makes the assessment of NYHA class much less reliable. The study was also too small to give reliable information on safety. The effects of trimetazidine on remodelling are of particular interest because it seems increasingly clear that drugs that increase ejection fraction and reduce ventricular volumes are likely to improve symptoms and prognosis in heart failure, in the absence of any other harmful, offsetting action. Consequently, the findings of Di Napoli and colleagues are potentially very important. Clearly, however, more information is needed. In precisely what type of patient are these effects obtained? Is it only in patients with angina, or only where there is demonstrable myocardial ischaemia, or is trimetazidine beneficial in all patients with coronary artery disease? This type of treatment may have a particular role in diabetics.^{6,7} Is there benefit in more advanced heart failure as these patients already demonstrate a switch from FFA to glucose oxidation?⁸ Are the effects on remodelling incremental to best available current treatment—that is, an ACE inhibitor, β blocker, and angiotensin receptor blocker, aldosterone blocker, or both? Testing the effect of trimetazidine in addition to a β blocker is especially important as it has been postulated that these drugs may also induce a metabolic shift, although the evidence is not strong.⁹

If the findings of Di Napoli and colleagues can be replicated and extended (and if there are no safety concerns), there would be a strong case for an outcome trial with trimetazidine (or a similar agent¹⁰) in patients with heart failure and coronary artery disease.

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