Trimetazidine: the future of cardiac function?

“...trimetazidine could represent a new therapeutic opportunity in the management of left ventricle dysfunction and remodeling in heart failure patients.”

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The continuous knowledge of the pathophysiological background of heart failure is fundamental in the management of this complex disease. Although there are considerable modern therapeutic advances, heart failure remains a leading cause of morbidity and mortality in developed [1] and increasingly in developing countries [2] with a 5-year mortality rate of approximately 50%, which exceeds that of many cancers [3]. The prognosis worsens with the advancement of heart failure and the mortality rate in patients in New York Heart Association (NYHA) class IV is as high as 50% per year. The mode of death depends mainly on the NYHA class. Patients with less advanced heart failure; more frequently die suddenly (arrhythmic death), while those in NYHA class IV are more likely to die of irreversible heart failure (pump failure) [4,5]. Early neurohumoral activation with sympathetic overdrive interplaying with progressive hemodynamic changes constitutes the main characteristic of heart failure independent of its etiology [6]. This unacceptably high residual mortality and morbidity has mandated a re-evaluation of cardiac biology with the aim to identify novel therapeutic approaches for heart failure.

Over the past 20 years, there has been considerable progress in the treatment of chronic heart failure with angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, β -receptor blockers and resynchronization therapy [7,8]. Current medical treatment of heart failure is mainly directed at fluid overload and neurohormonal activation. Diuretics, digoxin and inotropes treat fluid overload and improve hemodynamic; while ACE-inhibitors, angiotensin II receptor antagonists, β -blockers and aldosterone antagonists restrain neurohormonal activation [8]. Despite these treatments, there is usually an ineluctable progression of contractile dysfunction and continuing left ventricular remodeling.

Currently, new treatments for heart failure that act independently of mechanisms already targeted, are under investigation and emerging evidence suggests that myocardium dysfunction in heart failure is also the consequence of alterations in substrate metabolism [7]. In particular, there is evidence that in the failing heart, shifting metabolism away from a preference for fatty acid towards more carbohydrate oxidation can improve contractile function, slowing the ineluctable progression of pump failure and improving prognosis in patients with heart failure [9].

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Trimetazidine, an anti-ischemic or ‘cytoprotective’ agent acting via metabolic pathways, has proved to be effective in the treatment of chronic stable angina and, more recently, left ventricle dysfunction. This drug has an inhibitory effect on the enzyme 3-ketoacyl coenzyme A thiolase, which plays a critical role in the β -oxidation pathway in the myocardium [10]. As a result, there is a switch of cardiac metabolism from free fatty acid to glucose oxidation, which represents a more efficient metabolic pathway in terms of oxygen consumption and energy (adenosine triphosphate) production. Recent studies have outlined the potential benefits that trimetazidine may offer in myocardial dysfunction owing to its ability to increase utilization of glucose and lactate, improving oxygen consumption of the myocardium by 16–26% [11].

Many studies have been carried out to establish which factors increase mortality and morbidity in patients with ischemic heart disease and heart failure. Factors that have been demonstrated to be predictors of mortality are increasing age, history of diabetes mellitus or renal dysfunction, measures of higher functional disability such as NYHA class, lower left ventricular ejection fraction (LVEF), lower sodium concentrations and lower quality-of-life scores [12-14]. Recently, intense interest has emerged in the predictive value of plasma biochemical markers such as C-reactive protein, B-type natriuretic peptide (BNP) and cardiac troponin T [15,16]. A variety of clinical studies provided evidence that trimetazidine treatment could also positively influence these prognostic factors.

For all these reasons, a therapeutic approach using trimetazidine could positively influence left ventricle dysfunction and remodeling with potential prognostic relevance in heart failure patients.

On the basis of the hypothesis that free fatty acid inhibitors could act as metabolic modulators in the protection of ischemic myocardium, the effects of trimetazidine have been previously assessed in patients with ischemic cardiomyopathy. In these patients, mortality rate and quality-of-life are unsatisfactory and left ventricular dysfunction is the result of the progressive process of myocardial fibrosis, or hibernating or stunned myocardium. An early therapeutic management of hibernating and stunned myocardium is fundamental in ischemic cardiomyopathy, because they are potentially reversible conditions. Belardinelli *et al.* reported that trimetazidine exerted beneficial effects on chronically dysfunctional myocardium [17]. In patients with ischemic cardiomyopathy, a previous acute myocardial infarction, multivessel coronary artery disease and ventricular dysfunction (ejection fraction 33%), trimetazidine therapy (2 months) improved contractile response to low-dose dobutamine in chronically dysfunctional myocardium. Fragasso *et al.* demonstrated that trimetazidine restored the energetic status of myocardium in patients with heart failure [18]. In these patients, the phosphocreatine and adenosine triphosphate (PCr:ATP) ratio, an important index of energetic status, was similar to that in healthy individuals and significantly improved compared with that in a placebo group. These results appear particularly interesting, especially in view of previous evidence suggesting the PCr:ATP ratio to be a significant predictor of mortality [19]. The beneficial effects of trimetazidine in patients with ischemic cardiomyopathy are confirmed in longer

follow-up. Brottier *et al.* assessed the value of trimetazidine treatment with in patients with severe ischemic cardiomyopathy [20]. After 6 months of treatment, the patients reported a considerable improvement in symptoms and demonstrated a greater LVEF compared with the placebo group. These effects are also evident in long-term follow-up [21], in elderly and diabetic patients. Vitale *et al.* reported 47 patients (aged 78 ± 3 years) with ischemic cardiomyopathy who were treated with trimetazidine and achieved significant improvement in ejection fraction and quality of life [22]. Fragasso *et al.* reported an improvement in ejection fraction in diabetic patients with ischemic cardiomyopathy [23].

The cardioprotective effects of trimetazidine were also detected in patients with systolic dysfunction heart failure of different etiologies, not only that secondary to coronary artery disease [24]. Recently, Tuunanen *et al.* reported in 19 nondiabetic patients with idiopathic dilated cardiomyopathy that trimetazidine increase LVEF from 31 to 35% ($p = 0.027$); this increase was associated with a significant decrease of insulin resistance. In this way, the effects of trimetazidine could be related to an improvement of whole-body insulin sensitivity and glucose control, thus hypothetically countering the myocardial damage of insulin resistance [25].

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Trimetazidine exerts positive effects on the inflammatory status that characterizes ischemic cardiomyopathy and have been related to higher rates of readmission to hospital and mortality [26]. It has been also observed that trimetazidine was able to reduce the release of endothelin-1 in patients with heart failure [24]. Despite the recognized adaptive advantage of endothelin-1 in supporting the contractility of the failing heart, persistent increases in its expression in the failing heart have a pathophysiologically maladaptive aspect, and are associated with the severity of myocardial dysfunction [9]. In patients with left ventricular dysfunction, the plasma concentration of BNP is also significantly reduced during treatment with trimetazidine [27]. If we consider BNP as a marker of myocardial load, trimetazidine treatment could positively redirect the neurohormonal pathway in patients with

ischemic cardiomyopathy and reduce the progressive cellular damage and lost that characterizes the chronic evolution of left ventricle remodeling.

Trimetazidine is also able to increase the myocardial cell resistance to cardiac overload that usually occurs in patients with ventricular dilation or dysfunction. In patients with chronic heart failure, during acute decompensation myocardial cell damage, expressed as troponin T release, is significantly reduced and the direct correlation between BNP (index of cardiac load) and troponin T plasma concentrations – usually observed in heart failure patients – is lost [28]. This means increased cell resistance to injury.

All these results could contribute to explaining the reduction of ventricular remodeling and the preservation of left ventricle function during trimetazidine treatment. Although these findings are highly suggestive, it remains to be ascertained whether the benefits discussed above would translate in no doubt improved survival rates. The question of whether there are prognostic benefits during trimetazidine treatment in patients with heart failure is still under investigation and needs more clarifications. We know the prognostic value of an improvement in ejection fraction, NYHA class and biochemical markers in these patients but, at the moment, the prognostic relevance of trimetazidine is no more than speculative or fruit of an incomplete clinical experience. In patients with ischemic left ventricular dysfunction and multivessel coronary artery disease, El-Kady *et al.* reported positive effects of trimetazidine on prognosis: survival at

2 years was 92% among patients treated with trimetazidine and 62% among those treated with placebo [29]. In a *post hoc* analysis obtained from the 48-month extension of the Villa Pini d'Abruzzo trimetazidine trial, trimetazidine treatment reduced all-cause mortality (17 versus 39% in controls) and admission to hospital owing to heart failure (decreased by 47%) [30].

In summary, the correction of the metabolic alterations that characterize dilated cardiomyopathy and heart failure could represent a promising novel therapeutic approach useful in improving prognosis. The metabolic modulator trimetazidine represents the most studied and valued drug with positive effects in patients with chronic coronary artery disease and heart failure. Although its true relevance to prognosis needs to be ascertained by large multicenter, randomized, placebo-controlled trials, the selective inhibition of 3-KAT with trimetazidine could represent a new therapeutic opportunity in the management of left ventricle dysfunction and remodeling in heart failure patients.

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