

Effects of Vastarel MR on brain natriuretic peptide and cardiac troponin concentrations

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Abstract

Metabolic therapy represents an innovative approach to the treatment of coronary artery disease and heart failure. The metabolic modulator, trimetazidine (Vastarel MR), offers particular positive effects in reducing the cell loss and reorganization that characterize the process of left ventricle remodeling, and is useful in improving ischemic or failed cell metabolism. Correction of the metabolic alterations that characterize ischemic cardiomyopathy and heart failure represents a promising novel therapeutic approach useful in reducing left ventricle remodeling and improving the prognosis of patients suffering these conditions.

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Introduction

Coronary artery disease (CAD) and chronic congestive heart failure (CHF) represent major public health concerns that have a poor long-term prognosis [1] and, despite vigorous effort and financial input, few clinical tools have been developed to identify variables that have prognostic significance for patients suffering these conditions. The New York Heart Association (NYHA) functional classification, and several tests – including chest X-ray, electrocardiogram, ultrasound, radionuclide and magnetic resonance imaging, cardiopulmonary exercise, and hemodynamic measurements – are useful for estimating the severity and prognosis of CHF.

The deterioration of cardiac function in chronic CAD and CHF is strictly related to left ventricular remodeling, a pathologic process by which ventricular size, shape, and function are dysregulated by hemodynamic overload, neurohormonal activation (involving adrenergic nervous hyperactivity, the

renin–angiotensin system, and inflammatory cytokines), and genetic factors. The pathologic changes in cardiac myocytes and fibroblasts are an important component of cardiac remodeling [2,3], and biochemical markers of the pathophysiology of CHF might be helpful in monitoring its evolution and the development of remodeling, because they are usually easy to measure serially, without inter-observer variability.

Measurement of plasma concentrations of brain natriuretic peptide (BNP), an amino acid peptide secreted by the ventricular myocardium in response to myocardial load, is now increasingly being used as a tool for clinical diagnosis and prognosis in patients with CHF and CAD [4]. Other important biochemical markers are troponins, which are strictly related to the cell loss that characterizes ventricular remodeling after myocardial infarction, chronic ischemia, and pressure or volume overload – factors influencing the progression of left ventricular dysfunction [5]. In addition, norepinephrine (noradrenaline; a marker of adrenergic activity), renin, inflammatory cytokines,

C-reactive protein, and biochemical markers associated with collagen turnover may have significant roles in the pathophysiology [6–8].

Left ventricle remodeling in ischemic heart disease and heart failure

Cardiac remodeling is an important determinant of CHF progression. Hemodynamic overload, activation of the renin–angiotensin and sympathetic nervous systems, and inflammatory cytokines are believed to be implicated [1,2,9]. At cellular level, the most important factor influencing ventricular remodeling is progressive cell loss as a result of apoptotic or necrotic processes. This is the first stage in ventricular remodeling, in which the normal architecture of the heart wall is rearranged, with the replacement of contractile mass by noncontractile fibrous tissue. In addition to myocyte injury, the interstitium, fibroblasts, and collagen turnover also have important roles.

Ischemic injury has long been considered to result in necrotic tissue damage; however, in recent decades, studies have focused attention on apoptosis as a significant component of cell loss during reperfusion injury, myocardial infarction, and chronic ischemia [10,11]. Myocardial apoptosis has also been documented in response to a variety of other cardiac stresses, including pressure or volume overload, heart failure, and diabetic cardiomyopathy [12,13]. The most relevant clinical stimulants that initiate the process of apoptosis include pressure or volume overload, cellular calcium overload, oxygen-derived free radicals, increased concentrations of catecholamines, cytokines, and angiotensin II, and decreased coronary flow reserve [12–14].

The relevance of metabolic therapy in heart failure

The basic principle of current treatment in patients with heart failure with or without CAD is to modify myocyte dysfunction and to minimize the intensity of the lethal injury acting on the heart. Clinical interventions such as restoration of ischemia by pharmacological or interventional strategies, use of β -block-

ers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists may prevent, suppress, or restore cardiac dysfunction. However, the preservation of cells subjected to lethal injury remains an attractive goal, and inhibition of cardiac myocyte apoptosis by metabolic treatments may represent a novel approach for treatment of cardiac disease [9,15]. Available evidence suggests that the failing heart is an engine that is depleted of fuel. In other words, altered energetics plays an important part in the pathophysiology of heart failure. Various groups have pursued this energy-depletion hypothesis over the past 20 years and, today, energy metabolism in the heart is a topic of considerable interest.

Major metabolic changes occurring during the early hours of myocardial infarction include increased secretion of catecholamines and production of circulating free fatty acids (FFAs). Under normal conditions, the myocardium depends on aerobic metabolism, with FFAs as the preferred source of energy. During ischemia-reperfusion, FFA concentrations are greatly increased, and exert a toxic effect on the myocardium. This effect determines increased membrane damage, endothelial dysfunction, tissue inflammation, and decreased cardiac function. Decreasing plasma FFA concentrations and cardiac fatty acid oxidation, together with the stimulation of glucose and lactate uptake, might reduce these detrimental effects [9,15,16]. This might be achieved by the use of glucose–insulin–potassium solutions at the time of reperfusion [17], and by inhibiting fatty acid oxidation with 3-ketoacyl coenzyme A thiolase inhibitors, such as trimetazidine [9,15]. Currently, we have many remarkable experimental and clinical findings regarding the beneficial effects of metabolic treatment in CAD and heart failure. The drug studied most is trimetazidine. A variety of clinical studies of this drug have demonstrated that it offers a significant cardioprotection that is achieved through several mechanisms (*Table I*).

Plasma brain natriuretic peptide and troponin concentrations

In contrast to other neurohormones that exhibit increased concentrations in heart failure, natriuretic

Table I. Main cardioprotective effects of trimetazidine in patients with CAD, left ventricular dysfunction, or both.

- Improvement in metabolic efficiency: changing the source of ATP production to glucose oxidation, a more energetically efficient pathway
- Protection of endothelial function: increase in endothelial nitric synthase activity and nitric oxide availability; reduction in endothelin-1
- Preservation of mitochondrial functions: reduction in mitochondrial permeabilization
- Reduction of the myocardial inflammatory reaction: reduction of neutrophil infiltration and activation
- Reduction in necrotic and apoptotic cell death
- Limitation of accumulation of Na^+ and Ca^{2+} and intracellular acidosis
- Protection against toxicity induced by oxygen free radicals
- Improvement in insulin sensitivity and glucose concentrations

Focus on Vastarel MR

Effects of trimetazidine on biomarkers

peptides have an adaptive counter-regulatory role [18]. Plasma BNP concentrations are currently used as diagnostic and prognostic markers in patients with CHF [18]. It is particularly noteworthy that, in multivariate analyses, BNP and N-terminal proBNP (NT-proBNP) are stronger predictors of mortality than NHYA functional class, norepinephrine (adrenaline), left ventricular ejection fraction (LVEF), or age [19,20]. Serum BNP is also a valid marker in assessing the risk of ventricular tachycardia and, probably, sudden death, in patients with ischemic or non ischemic cardiomyopathy [21]. Tapanainen et al [22] showed that increased serum BNP concentration provided information on the risk of arrhythmic death among the survivors of acute myocardial infarction, independently of LVEF, and should therefore be used as an additive marker to identify those patients who may benefit the most from defibrillator implantation.

Serum troponins are other important prognostic markers in patients with dilated cardiomyopathy [23–25]. The cardiac troponins are part of the troponin–tropomyosin complex in thin filaments of heart muscle myofibrils. Troponins do not occur outside cells; therefore, their occurrence in blood is a sensitive and specific indicator of heart muscle cell damage. Nellessen et al [23] assessed the usefulness of tests for troponin I (TnI) as prognostic indicators in patients with CHF. Miller et al [24] demonstrated that increases in the concentrations of troponin T (TnT) and BNP in patients with CHF are connected with an increased risk of death, heart transplant, or admission to hospital. The group at greatest risk included patients in whom an increase in both TnT and BNP was observed. Sato et al [25] confirmed that persistently increased concentrations of TnT in patients with dilated cardiomyopathy indicate that degeneration of myocytes is in progress, which is connected with the deterioration in the patients' clinical condition. Combining the measurements of BNP as an index of myocardial load and TnT as an index of myocyte injury is of particular interest in patients with heart failure. Measuring both BNP and TnT at the time of the patient's admission to hospital might identify a group of patients with acute heart failure who have the poorest prognosis [26].

Various studies have provided evidence that metabolic treatment with trimetazidine could positively influence the prognosis and quality of life of patients with CAD and CHF [9] and reduce left ventricular remodeling and plasma concentrations of BNP and TnT [27]. In 50 patients with stable ischemic cardiomyopathy after 6 months of trimetazidine treatment, we showed a significant improvement in functional capacity (6 min walking test) associated with a significant reduction in plasma BNP concentration (the latter was significantly increased in controls); TnT concentrations also reduced significantly during trimetazidine treatment, whereas they were un-

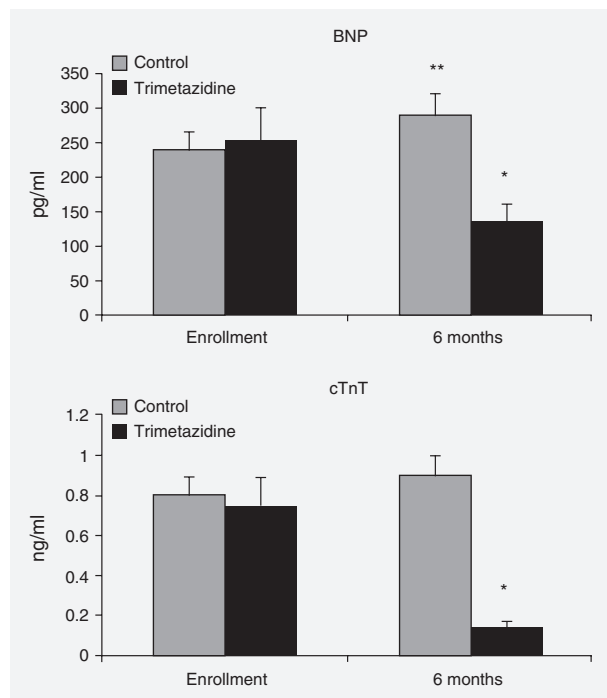


Figure 1. Changes in plasma concentrations of (a) brain natriuretic peptide (BNP) and (b) cardiac troponin T (cTnT) in patients with stable ischemic cardiomyopathy after 6 months of treatment with trimetazidine (60 mg/day; $n=25$) or no treatment (Control; $n=25$). Data are presented as mean and SD. * $P<0.001$ compared with control; ** $P<0.02$ compared with baseline. (From Di Napoli et al [27], with permission.)

changed in the control group (Figure 1) [27]. Fragasso et al [28] obtained similar results in 55 patients with heart failure and left ventricular dysfunction of various etiologies. If we consider BNP to be a marker of myocardial load, these findings confirm that trimetazidine treatment has a positive affect on the neuro-hormonal pathway in patients with ischemic cardiomyopathy and reduces the cellular damage that characterizes chronic evolution of left ventricle remodeling. Another positive mechanism of action of trimetazidine is its ability to increase myocardial resistance to injury in patients with ventricular dilatation or dysfunction. During acute decompensation in patients with chronic heart failure, myocardial cell damage, expressed as the release of TnT, is significantly reduced, and the direct correlation between plasma concentrations of BNP (cardiac load) and TnT (cardiac damage), observed in CHF patients, is lost [9]. All these data could help to explain the reduction in ventricular remodeling and the preservation of left ventricle function that are observed during treatment with trimetazidine. ■

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