

# Effects of trimetazidine on hormones and the heart

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## Abstract

Trimetazidine is a well-known, clinically effective antianginal agent recommended by guidelines for the treatment of stable angina pectoris. There is also substantial evidence for its benefit in patients with heart failure. Natriuretic peptides are markers of myocardial load and findings from recent studies suggest that trimetazidine treatment has a positive effect on this neurohormonal pathway in patients with ischemic heart disease or heart failure. ■ *Heart Metab.* 2015;66:24-26

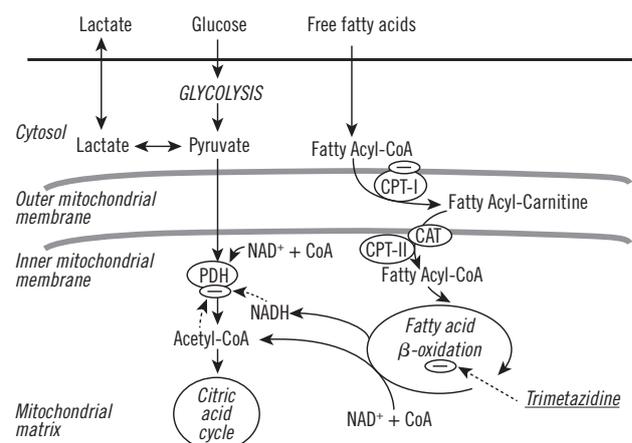
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Coronary artery disease (CAD) and congestive heart failure (CHF) represent two major public health problems that impair quality of life and reduce longevity. The impairment of cardiac function in chronic CAD and CHF is related to left ventricular remodeling, a pathologic process by hemodynamic overload and neurohormonal activation.<sup>1</sup> The heart exerts an endocrine function where both atria and ventricles are able to produce cardiac natriuretic hormones. The activation or deactivation of the cardiac natriuretic hormone system is almost always the result of one or more physiological or pathological changes. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted from the heart as a result of direct wall stress, to protect the human body from volume overload<sup>2</sup> and also to inhibit the renin-angiotensin system, endothelin secretion, and sympathetic activity.<sup>3</sup> Measurement of plasma concentrations of natriuretic peptide is now increasingly being used as a tool for clinical diagnosis and prognosis in patients with CHF and CAD.<sup>4</sup>

## Trimetazidine's mechanism of action

In the heart, adenosine-5'-triphosphate (ATP) is produced primarily by the metabolism of free fatty

acids (FFAs) and carbohydrates.<sup>5</sup> FFA oxidation provides more energy, but it is associated with increased oxygen consumption. Trimetazidine is a partial inhibitor of the  $\beta$ -oxidation enzyme long-chain 3-ketoacyl coenzyme A thiolase (3-KAT) activity, the final enzyme in the FFA  $\beta$ -oxidation pathway (Figure 1).<sup>6,7</sup> It increases pyruvate dehydrogenase



**Fig. 1** Diagram illustrating the site of action of trimetazidine and various cardiac metabolic modulators.

**Abbreviations:** CAT, carnitine-acylcarnitine translocase; CoA, coenzyme A; CPT, carnitine palmitoyltransferase; NAD<sup>+</sup>, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); PDH, pyruvate dehydrogenase.

**From reference 7:** Sabbah HN, Stanley WC. *Heart Fail Rev.* 2005;10(4):281-288. © 2006, Springer Science and Business Media, LLC.

### Abbreviations

**ANP:** atrial natriuretic peptide; **ATP:** adenosine-5'-triphosphate; **BNP:** brain natriuretic peptide; **CAD:** coronary artery disease; **CHF:** congestive heart failure; **FFA:** free fatty acids; **NYHA:** New York Heart Association

activity and the metabolic rate of glucose.<sup>8</sup> This results in decreased oxygen consumption, hydrogen ion production, intracellular acidosis, and reduced calcium ion accumulation. Trimetazidine reduces myocardial injury caused by free radicals, therefore modulates the inflammatory response. In this way, trimetazidine protects the whole myocardium against necrotic and apoptotic cell death and reduces the remodeling process.

### Trimetazidine in coronary artery disease

Existing data support the use of drugs that optimize cardiac energy metabolism such as trimetazidine for the treatment of patients with CAD.<sup>9,10</sup> The VASCO study is the largest randomized controlled study conducted with trimetazidine. Patients with stable angina receiving 50 mg of atenolol were randomized to the addition of trimetazidine MR 70 mg or 140 mg, or placebo for a 12-week period. In the cohort of all chronic stable angina patients, trimetazidine significantly improved total exercise duration compared with baseline and placebo.<sup>11</sup> Recent European Society of Guidelines on stable angina pectoris recommended that trimetazidine may be used as an add-on drug after  $\beta$ -blockers.<sup>12</sup>

Major metabolic changes occur during the early hours of myocardial infarction and 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. Trimetazidine reduces ischemia/reperfusion damage following ischemia and preserves myocardial contractile function.<sup>13</sup> Decreasing plasma FFA concentrations and cardiac fatty acid oxidation, together with the stimulation of glucose and lactate uptake, might reduce these detrimental effects.<sup>14</sup> Demirelli et al assessed the impact of treatment with trimetazidine in patients with non-ST segment elevation myocardial infarction undergo-

ing percutaneous coronary intervention.<sup>15</sup> Forty-five patients were randomly assigned to receive either placebo or trimetazidine. In patients on trimetazidine at 1-month follow-up, a considerable improvement in left ventricular end-diastolic volume was reported and BNP levels decreased compared with patients on placebo. The authors concluded that the beneficial effects of percutaneous coronary intervention (PCI) may be reinforced with a combination of PCI and trimetazidine treatment.

### Trimetazidine in heart failure

Natriuretic peptide is used in the diagnosis, monitoring, and prognosis of patients with congestive heart failure.<sup>16</sup> Its concentration falls in patients with decompensated heart failure after treatment, suggesting that measurement of plasma natriuretic peptide may be helpful in titrating therapy.<sup>17</sup> The plasma measurement of natriuretic peptide is also used in the diagnosis and prognosis of patients with CAD. Increased natriuretic peptide was found to be related to ischemia.<sup>18</sup>

Trimetazidine has documented effects on improving the left ventricular function, exercise tolerance, and New York Heart Association (NYHA) class. A recent study demonstrated that short-term trimetazidine treatment in patients with ischemic cardiomyopathy improves exercise tolerance and reduces plasma level of BNP. The study involved 50 patients with ischemic cardiomyopathy; 25 patients were assigned to receive conventional treatment plus trimetazidine, while the remaining 25 patients constituted the control group. After a 6-month follow-up, both groups achieved an insignificant reduction in NYHA class. The group receiving trimetazidine demonstrated a considerable reduction in BNP levels and cardiac troponin T, while the control group showed increased plasma BNP levels, with no significant changes in cardiac troponin T levels. Trimetazidine administration also resulted in a significant improvement in exercise tolerance assessed with a 6-minute walk test, however, it was not associated with a significant improvement in left ventricular systolic function, at baseline, and after 1 month and 6 months, respectively.<sup>19</sup> Fragasso et al obtained similar results in 55 patients with heart failure and left ventricular dysfunction of various etiologies.<sup>20</sup> Zhang et al presented a meta-analysis on the use of trimetazidine in CHF patients.<sup>21</sup> Sixteen randomized

studies were evaluated, with 884 patients in the study group. This meta-analysis demonstrated that the use of trimetazidine was associated with improved left ventricular ejection fraction, increased exercise tolerance, reduced NYHA class, decreased left ventricle volume and plasma BNP levels, and a reduced rate of cardiovascular hospitalizations.

ANP, another biomarker of heart failure, appears to be noninferior to BNP for diagnosis of acute heart failure and also has prognostic value in patients with CHF.<sup>22</sup> The rise in ANP secretion can be reversed by successful treatment of heart failure. Morgan et al, using an experimental heart failure model, additionally demonstrated that treatment with trimetazidine over a 12-week period reduced the levels of ANP.<sup>23</sup>

## Conclusion

In conclusion, trimetazidine is a well-known, clinically effective drug for the treatment of stable angina pectoris. Evidence for its benefit in patients with heart failure is also substantial. Considering natriuretic peptides to be a marker of myocardial load, findings from recent studies suggest that trimetazidine treatment has a positive effect on this neurohormonal pathway in patients with ischemic heart disease or heart failure. ■

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