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Metabolic Modulators in Cardioprotection: A Focus on Trimetazidine

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Abstract

Cardiovascular diseases remain a significant health burden worldwide, necessitating the development of effective cardioprotective strategies. Central to this pursuit is the recognition of metabolic dysregulation as a key contributor to the pathogenesis of cardiovascular diseases, particularly in the context of aging and modern lifestyle factors.

Metabolic modulators, such as trimetazidine, have emerged as promising therapeutic agents by optimizing cardiac energy substrate utilization and enhancing metabolic efficiency. Trimetazidine demonstrates cardioprotective properties by inhibiting fatty acid oxidation and promoting glucose oxidation, especially under ischemic conditions where oxygen supply is limited. This metabolic shift enhances myocardial efficiency, reduces the likelihood of acidosis, and mitigates the accumulation of toxic fatty acid metabolites. Pre-clinical studies and clinical trials have demonstrated the efficacy of trimetazidine in a range of cardiac conditions, including chronic stable angina, heart failure, and diabetic cardiomyopathy, resulting in improvements in symptoms, exercise capacity, and cardiac function.

Through its ability to address underlying metabolic inefficiencies, trimetazidine offers a promising adjunct therapy for patients with cardiovascular diseases, particularly those inadequately controlled by first-line treatments. This manuscript underscores the important role of metabolic modulation in the management of cardiovascular diseases and highlights trimetazidine as a valuable therapeutic option in the armamentarium against cardiac diseases.

Key words: cardioprotection, trimetazidine

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Introduction

The pursuit of effective cardioprotection is one of the focal points in developing future therapeutic strategies against cardiovascular diseases. The incidence and impact of heart diseases continue to grow, driven, at least in part, by the metabolic dysregulation associated with aging and modern lifestyle. This metabolic dysregulation characterized by impaired glucose and lipid metabolism, insulin resistance, and abnormal energy substrate utilization by the heart, plays a crucial role in the development of different heart diseases, including diabetic cardiomyopathy, ischemic heart disease, and heart failure (1).

Against this backdrop, metabolic modulators have emerged as a promising class of cardioprotective agents. These compounds are designed to optimize energy substrate utilization by the heart and improve metabolic efficiency. Among these, trimetazidine stands out as a main medication whose cardioprotective properties could be exploited in conditions where cardioprotection would be beneficial (2).

Trimetazidine acts by inhibiting fatty acid oxidation and promoting glucose oxidation. This shift in energy substrate preference is especially beneficial under ischemic conditions, where oxygen supply is limited and the heart's ability to utilize fatty acids is compromised. By enhancing glucose oxidation, trimetazidine improves the efficiency of oxygen utilization by the heart, which in turn enhances cardiac function. By modulating metabolic pathways, metabolic modulators like trimetazidine address the disease at a fundamental level, offering improvement in cardiac efficiency and protecting against the detrimental effects of ischemia and metabolic stress (3). This approach underscores the importance of energy metabolism in heart disease and opens up new avenues for the development of targeted, mechanism-based therapies addressing the underlying causes of cardiac dysfunction.

Cardiac Metabolism and Disease

The heart demands a continuous supply of energy to sustain its vital function. Under physiological conditions, the heart predominantly utilizes fatty acids (approximately 60-70%) and glucose (approximately 30-40%) for energy production, while ketone bodies, lactate, and amino acids play minor roles. This allows the heart to adapt to varying conditions of supply and demand. Energy is generated through mitochondrial oxidative phosphorylation which produces adenosine triphosphate (ATP), the primary energy currency of the cell. The efficiency of these metabolic processes is important for the maintenance of cardiac function, especially during increased workload or stress (4).

In the context of cardiac diseases, such as coronary artery disease, heart failure, and diabetic cardiomyopathy, metabolic dysregulation becomes a crucial issue. Under these conditions, the heart's ability to switch between energy substrates is compromised, which leads to an overreliance on glucose metabolism through anaerobic glycolysis, a less efficient means of ATP production that contributes to the accumulation of lactate and subsequent

acidosis (4). Furthermore, conditions like insulin resistance and diabetes exacerbate metabolic inflexibility, impairing cardiac efficiency and contractility. The consequences of metabolic dysregulation in the heart include energy starvation, increased oxidative stress, and accumulation of toxic metabolites. Thus, the disruption of normal metabolic pathways is a central player in the progression and severity of cardiac diseases (4-6).

Given the critical role of metabolic dysregulation in cardiac diseases, targeting metabolic pathways looks like a reasonable and promising avenue for therapy. Trimetazidine acts by inhibiting fatty acid oxidation, thereby shifting the metabolic substrate preference towards glucose oxidation. This shift seems to improve the efficiency of oxygen utilization, enhance ATP production, and reduce the accumulation of pro-oxidant fatty acid metabolites. By optimizing substrate utilization and improving metabolic flexibility, metabolic modulators enhance cardiac function, alleviate symptoms, and potentially slow the progression of cardiac diseases (2, 3).

Trimetazidine and metabolic modulation

The primary mechanism of action of trimetazidine involves the inhibition of long-chain 3-ketoacyl CoA thiolase (LC 3-KAT), an enzyme involved in the β-oxidation of fatty acids. By inhibiting this enzyme, trimetazidine shifts myocardial energy substrate preference from fatty acids to glucose (2, 3; Figure 1). This shift is beneficial for several reasons:

1. It improves oxygen efficiency: glucose oxidation requires less oxygen per molecule of ATP produced compared to fatty acid oxidation. In the context of ischemic conditions, where oxygen supply is limited, this shift can improve myocardial efficiency and reduce ischemic injury (2, 3).
2. It has been shown that under ischemic conditions trimetazidine activates adenosine monophosphate-activated protein kinase (AMPK) and extracellular-signal regulated protein kinases 1 and (ERK1/2) signaling pathways (7); both signaling pathways are well known to mediate cardioprotection (8). In addition, it has been shown that this compound regulates the expression of mitochondrial calcium uniporter by reactive oxygen species/ nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway inhibition (9).
3. It reduces the probability of acidosis: Glucose oxidation produces fewer protons than fatty acid oxidation, which can help mitigate acidosis during ischemia (10).
4. It decreases metabolizing of intracellular fatty acid: High levels of fatty acid metabolites can be toxic to cardiac cells. By reducing fatty acid oxidation, trimetazidine may decrease the accumulation of these metabolites and protect the myocardium from lipotoxicity. Trimetazidine has been found to provide a cardioprotective effect in patients with angina or cardiac dysfunction with diabetes mellitus (2, 3).
5. It has been shown that trimetazidine prevents diabetic cardiomyopathy by inhibiting NADPH oxidase 2/transient receptor potential cation channel

subfamily C member 3 (Nox2/TRPC3)-induced oxidative stress and by downregulating the expression of caspase-12, a protein associated with apoptosis (11, 12).

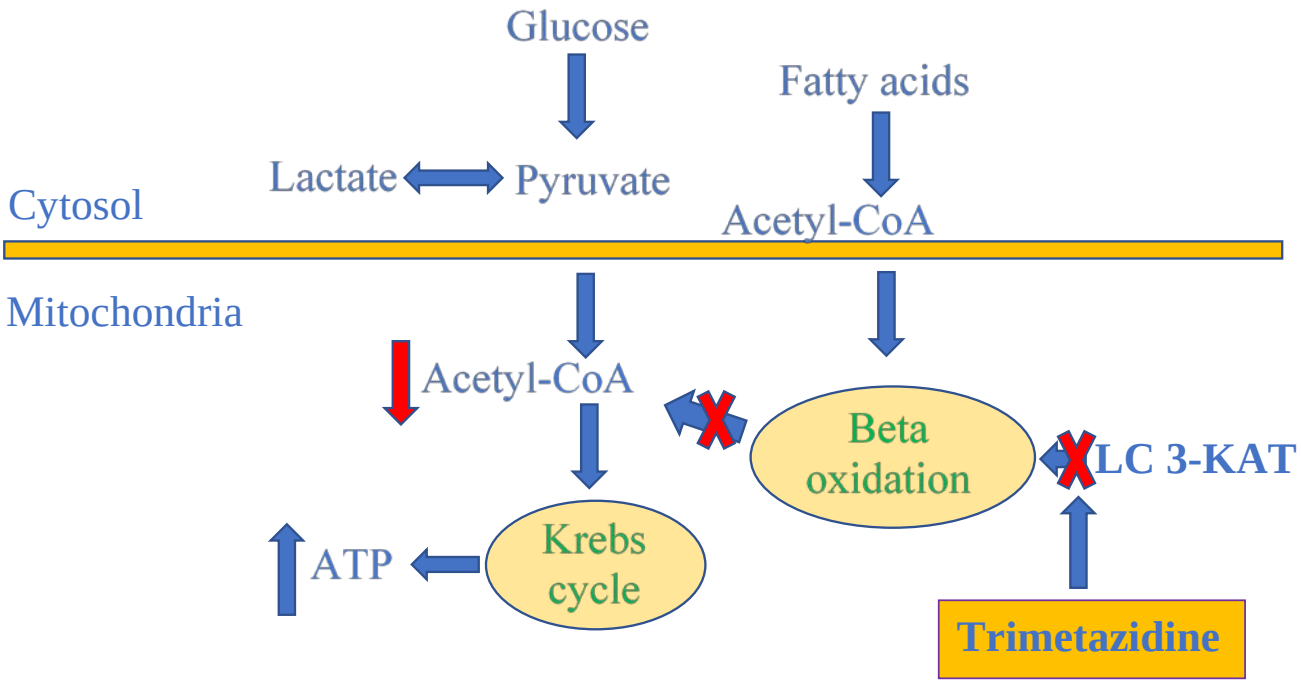

Figure 1. **The mechanism underlying trimetazidine. Trimetazidine inhibits LC 3-KAT, an enzyme catalysing β-oxidation of fatty acids. In turn, this decreases the production of Acetyl-CoA originating from fatty acids, shifting myocardial energy substrate preference from fatty acids to glucose.**

Slika 1. **Mehanizam dejstva trimetazidina. Trimetazidin inhibiše LC 3-KAT, enzim koji katalizuje β-oksidaciju masnih kiselina. Ovo smanjuje proizvodnju Acetil-CoA poreklom iz masnih kiselina, preusmeravajući energetski supstrat miokarda sa masnih kiselina na glukozu.**

For these reasons, several clinical studies have explored the potential benefits of trimetazidine, an inhibitor of free fatty acids oxidation that shifts cardiac and muscle metabolism to glucose utilization. Because of its mechanism of action, trimetazidine has been found to provide a cardioprotective effect in patients with angina, diabetes mellitus, and left ventricular (LV) dysfunction. The mechanisms underlying trimetazidine action and their benefits are depicted in Table I.

Table I Mechanisms underlying trimetazidine action and their benefits

Tabela I Mehanizmi dejstva trimetazidina i njihovi pozitivni efekti

Mechanism/Benefit	Description	References
Inhibition of LC 3-KAT	Trimetazidine inhibits long-chain 3-ketoacyl CoA thiolase (LC 3-KAT), shifting myocardial energy substrate preference from fatty acids to glucose.	(2), (3)
Improves oxygen efficiency	Glucose oxidation requires less oxygen per molecule of ATP produced compared to fatty acid oxidation, improving myocardial efficiency and reducing ischemic injury.	(2), (3)
Activation of AMPK and ERK1/2	Under ischemic conditions, trimetazidine activates AMPK and ERK1/2 signaling pathways, which mediate cardioprotection.	(7), (8)
Regulation of mitochondrial calcium uniporter	Trimetazidine regulates the expression of mitochondrial calcium uniporter by inhibiting the ROS/NFκB pathway.	(9)
Reduces probability of acidosis	Glucose oxidation produces fewer protons than fatty acid oxidation, helping to mitigate acidosis during ischemia.	(10)
Decreases metabolizing of intracellular fatty acids	By reducing fatty acid oxidation, trimetazidine decreases the accumulation of toxic fatty acid metabolites, protecting the myocardium from lipotoxicity.	(2), (3)
Prevents diabetic cardiomyopathy	Trimetazidine prevents diabetic cardiomyopathy by inhibiting Nox2/TRPC3-induced oxidative stress and downregulating caspase-12, a protein associated with apoptosis.	(11), (12)
Cardioprotective effects	Trimetazidine provides cardioprotective effects in patients with angina, diabetes mellitus, and left ventricular (LV) dysfunction.	(2), (3)

Clinical implications and use

Trimetazidine has been studied in many cardiac conditions, including chronic stable angina. It has been shown that trimetazidine improves exercise capacity and reduces angina frequency. This effect is not associated with changes in heart rate or blood pressure, which underscores the metabolic rather than hemodynamic basis of its action. There are studies demonstrating the beneficial effect of trimetazidine in heart failure, diabetic cardiomyopathy, and reperfusion injury. In heart failure, the beneficial effect seems to be due to the improvement of the energy metabolism in the failing heart, which helps to enhance contractile function and exercise tolerance. Trimetazidine seems to be particularly useful in diabetic cardiomyopathy, where metabolic modulation counteracts cardiac dysfunction induced by metabolic disturbances. In reperfusion, there is evidence to suggest that trimetazidine reduces reperfusion injury by protecting cardiomyocytes (2, 3, 13-17). Numerous clinical trials have assessed the efficacy of trimetazidine in various cardiac conditions, leading to generally accepted findings. In patients with chronic stable angina, trimetazidine has been shown to significantly reduce angina attacks and improve exercise tolerance. The TRIMPOL II trial demonstrated that patients receiving trimetazidine experienced fewer angina episodes and required less nitroglycerin, with improved exercise capacity compared to the placebo group (18-20). There are clinical trials that have explored trimetazidine's effects on heart failure, with studies indicating improvements in left ventricular function and exercise capacity. It has been shown that trimetazidine led to an increase in left ventricular ejection fraction and an improvement in the New York Heart Association (NYHA) functional class (21). The cardioprotective effect of trimetazidine was also demonstrated in diabetic patients (22, 23).

In the 2024 European Society of Cardiology (ESC) Guidelines on Chronic Coronary Syndromes (CCS), trimetazidine is addressed primarily within the context of antianginal therapy (24). Thus, trimetazidine is recommended as a second-line antianginal agent that is intended for use in patients who cannot tolerate first-line medications such as beta-blockers or calcium channel blockers (CCBs). It is recommended that trimetazidine, along with long-acting nitrates or ranolazine, should be considered as an add-on therapy in patients who have inadequate symptom control while on beta-blockers and/or CCBs. Moreover, in selected patients, trimetazidine may be combined with a beta-blocker or a CCB as part of initial combination therapy. Trimetazidine is listed alongside nicorandil, ranolazine, and ivabradine as an option for second-line therapy to reduce angina frequency and improve exercise tolerance. It is fair to say that trimetazidine is positioned as a valuable second-line agent in the antianginal regimen for CCS.

However, it should be acknowledged that trimetazidine is associated with some significant adverse effects, including dizziness, headache, abdominal pain, diarrhea, dyspepsia, nausea, vomiting, constipation, asthenia, rash, pruritus and urticaria. In addition to these common side effects, more serious adverse effects have also been described, including palpitations, extrasystoles, tachycardia, arterial hypotension, orthostatic hypotension, flushing, agranulocytosis, thrombocytopenia/thrombocytopenic purpura, hepatitis, Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability,

restless leg syndrome, other movement disorders, insomnia and drowsiness. Trimetazidine is contraindicated in patients who are allergic to it and any of its excipients, in patients with Parkinson's disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders, and in patients with severe renal impairment. Trimetazidine warnings and precautions include exacerbation of movement disorders, and regular investigation for tremors, rigid posture, slow movements, and shuffling gait is required. If these symptoms occur, trimetazidine needs to be discontinued and a neurologist should be consulted if such symptoms persist beyond 4 months. There is also a risk of falls due to gait instability or orthostatic hypotension (25).

It should also be pointed out that trimetazidine, while being registered in several countries in Europe and Asia, has not been registered in the USA and the UK. The absence of trimetazidine from the UK and US markets is probably due to a combination of several factors including safety concerns, commercial viability assessments, and strategic decisions by the drug's manufacturers.

In addition, it should be mentioned that trimetazidine has been recognized as a doping agent by the World Anti-Doping Agency (WADA). Its inclusion on the list of doping drugs is primarily due to its potential performance-enhancing effects. As it has already been discussed, trimetazidine optimizes cellular energy metabolism, and by promoting more efficient energy production it delays the onset of muscle fatigue, resulting in improved endurance during prolonged physical activities. Trimetazidine-induced improvement in myocardial energy metabolism results in a more efficient heart that can sustain higher levels of physical activity with less strain, which would particularly benefit endurance athletes.

Conclusion

The importance of metabolic modulation through agents like trimetazidine lies in its ability to address the underlying metabolic inefficiencies that contribute to cardiac diseases, which offers a pathway to improved cardiac function. In addition to pre-clinical studies demonstrating the beneficial effects of trimetazidine in coronary heart disease, heart failure, and diabetic cardiomyopathy, there is also clinical evidence supporting the usefulness of this medication in these conditions. Through many studies and trials, trimetazidine has demonstrated its efficacy in reducing symptoms, enhancing exercise capacity, and, in some cases, positively impacting hospitalization rates and overall quality of life for patients with cardiovascular diseases. Thus, it is fair to conclude that trimetazidine could be used as an adjunct therapy, particularly for patients with angina pectoris who are not adequately controlled by or are intolerant to first-line antianginal agents.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

QD wrote, reviewed, and edited the original draft.

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Metabolički modulatori u kardioprotekciji sa fokusom na trimetazidin

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Kratak sadržaj

Kardiovaskularne bolesti i dalje predstavljaju značajan zdravstveni teret širom sveta, što zahteva razvoj efikasnih strategija kardioprotekcije. Za postizanje ovog cilja od ključnog značaja je prepoznavanje metaboličke disregulacije kao ključnog faktora u patogenezi kardiovaskularnih bolesti, posebno u kontekstu starenja i savremenih faktora načina života.

Metabolički modulatori, poput trimetazidina, uočeni su kao obećavajući terapijski agensi koji optimizuju korišćenje energetskih supstrata u srcu i povećavaju metaboličku efikasnost. Trimetazidin ispoljava kardioprotektivna svojstva inhibicijom oksidacije masnih kiselina i podsticanjem oksidacije glukoze, posebno u ishemijskim uslovima kada je snabdevanje kiseonikom ograničeno. Ova metabolička promena povećava efikasnost miokarda, smanjuje verovatnoću pojave acidoze i ublažava nakupljanje toksičnih metabolita masnih kiselina. Pretkliničke studije i klinička ispitivanja pokazala su efikasnost trimetazidina u nizu srčanih stanja, uključujući hroničnu stabilnu anginu, srčanu insuficijenciju i dijabetičku kardiomiopatiju, što je rezultiralo poboljšanjem simptoma, kapaciteta za vežbanje i funkcije srca.

Zahvaljujući svojoj sposobnosti da rešava osnovne metaboličke neefikasnosti, trimetazidin predstavlja obećavajuću dopunsku terapiju za pacijente sa kardiovaskularnim bolestima, posebno za one kod kojih lekovi prvog izbora nisu dovoljno efikasni. Ovaj rad naglašava važnu ulogu metaboličke modulacije u lečenju kardiovaskularnih bolesti i ističe trimetazidin kao vrednu terapijsku opciju u borbi protiv srčanih oboljenja.

Ključne reči: kardioprotekcija, trimetazidin