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Trimetazidine effects on oxidative damage

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Abstract

Trimetazidine is an anti anginal medication and ensures the proper functioning of transmembrane ionic channels by maintaining intracellular ATP production in ischemic conditions. Trimetazidine prevents the accumulation of calcium in cardiomyocytes, adjusts cellular acidosis, and decreases production of free oxygen radicals. Trimetazidine blocks long chain 3-ketoacyl coenzyme A thiolase activity, thereby shifting ATP production more towards glucose oxidation instead of fatty acid β-oxidation during myocardial ischemia. By inhibiting fatty acid β-oxidation, fewer free radicals are formed in the cardiomyocytes with more efficient oxygen consumption and ATP production, resulting in recovery of myocardial contractile function and inhibition of malignant arrhythmias. Moreover, cardiac enzymatic activities such as phosphorylase and ATPase increased significantly in ischemic areas with trimetazidine pretreatment before myocardial ischemia. Protective effects of trimetazidine by increasing ventricular fibrillation threshold during coronary artery occlusion were consistent in animal studies. ■ Heart Metab; 2013;60:27–29

Keywords: Myocardial infarction; oxidative damage; trimetazidine.

Introduction

Trimetazidine is an anti-ischemic metabolic drug used for patients with angina pectoris [1], and trimetazidine increases myocardial glucose utilization by inhibiting fatty acid oxidation [1, 2]. Some studies have revealed that trimetazidine improves left ventricular contractile function in patients with heart failure, thereby improving NYHA functional class and left ventricular function [3, 4]. Trimetazidine has been known as a "metabolic agent" because it ensures the proper functioning of transmembrane ionic channels by maintaining intracellular ATP production in ischemic conditions. Trimetazidine inhibits long chain 3-ketoacyl coenzyme A (CoA) thiolase activity, thereby maintaining ATP production in ischemic cardiomyocytes [5]. By preventing fatty acid β-oxidation, the ba-lance between ATP demand and supply can be maintained in patients with ischemic heart disease. During the process of myocardial ischemia, reactive oxygen species (ROS) such as superoxide anion and hydroxyl radicals accumulate in ischemic cardiomyocytes, resulting in damage to mitochondria and ultimately leading to apoptotic cell death [6, 7].

Oxidative stress and myocardial ischemia

Cumulative oxidative stress could cause various diseases such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases [8]. Oxidative damage has been implicated in oxygen reperfusion injury following coronary ischemia. Large amount of ROS produced together with calcium overload after postischemic reperfusion damages mitochondrial membrane and increases its permeability [1, 2, 9]. Mitochondrial damage with ROS can lead to

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Abbreviations

ATP: Adenosine-5'-triphosphate; **CoA:** coenzyme; **ROS:** reactive oxygen species.

electrical instability with increasing chance of ventricular fibrillation. Antioxidants such as vitamins, superoxide dismutase plus catalase, and N-acetylcysteines have been used to reduce ROS burden after myocardial ischemia [10, 11]. Trimetazidine, acting as a potent antioxidant during myocardial ischemia, reduces ROS thereby stabilizing mitochondrial integrity. Properly functioning mitochondria, which are energy power plants in the cardiomyocytes, contribute in decreasing myocardial infarct size after ischemic injury, subsequently reducing the incidence of malignant ventricular arrhythmias (*Figure 1*).

During myocardial ischemia, ATP production shifts towards fatty acid oxidation over glucose oxidation [2, 12]. ATP generation shifting towards fatty acid oxidation during myocardial ischemia produces less energy with accumulation of lactate and proton responsible for acidosis [1, 13]. Increased fatty acid oxidation results in increased mitochondrial damage, resulting in decreased myocardial contractile function. Trimetazidine comes into play during myocardial ischemia by blocking long chain 3-ketoacyl CoA thiolase activity, thereby shifting ATP production more towards glucose oxidation instead of fatty acid β-oxidation [14]. By inhibiting fatty acid β-oxidation, fewer free radicals are formed in the cardiomyocytes with more efficient oxygen consumption and ATP production, resulting in the recovery of myocardial contractile function and inhibition of malignant arrhythmias. Trimetazidine not only inhibits fatty acid β-oxidation, but also increases glutathione peroxidase, which is known as an antioxidant enzyme [1]. Mitochondrial structure and function can be maintained by preventing fatty acid β-oxidation and ROS production, and the beneficial effects of trimetazidine translate into a decrease in myocardial infarct size of more than 20% [1, 2]. Moreover, during postischemia reperfusion after myocardial ischemia, fatty acids such as palmitate can damage the myocardial contractile function by inducing mitochondrial uncoupling [2]. Mitochondrial uncoupling not only decrease ATP production but also promotes the development of ROS during myocardial ischemia. Palmitate induces the production of ascorbyl free radicals during the reperfusion period with subsequent mitochondrial damage and free radical formation [2]; however, trimetazidine pretreatment was shown to prevent ascorbyl free radical release during the postischemic period in rat hearts [2]. The release of ascorbyl free radical was associated with the production of oxygen free radicals during postischemic reperfusion, and was negatively correlated with cardiac contractile function [2]. Trimetazidine at high concentration competes with cytochrome c in clearing superoxide radicals produced by xanthine oxidase [2].

Cardioprotective effects of trimetazidine

Trimetazidine prevents ischemic damage to cardiomyocytes by preserving mitochondrial structure and function, and the production of ROS has been re-

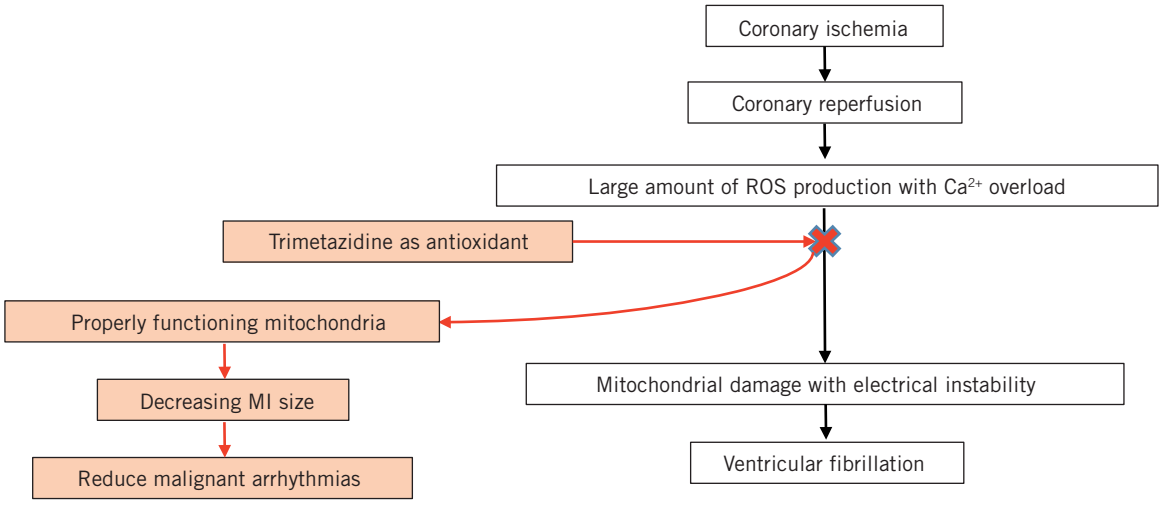

Fig. 1 *Trimetazidine reduces reperfusion myocardial injury by reducing mitochondrial damage. MI=myocardial infarction.*

duced by more than 30% with a 2-fold increase of oxidative phosphorylation [1]. In an experiment with swine, the effects of trimetazidine 20 mg immediate release and trimetazidine 35 mg modified release administered twice a day for four consecutive days were compared against placebo on ventricular fibrillation susceptibility during a 1-minute ischemia and on the protection of mitochondrial structure and function [1]. Ischemic areas were significantly reduced in pigs treated with trimetazidine, and mitochondrial structure and function were preserved after ischemic events in both trimetazidine-treated groups. The ventricular fibrillation threshold is lowered during myocardial ischemia, but trimetazidine increases the ventricular fibrillation threshold during ischemic conditions, thereby preventing malignant arrhythmia in ischemic heart disease [15, 16]. Trimetazidine prevents the accumulation of calcium in cardiomyocytes, adjusts cellular acidosis, and decreases the production of free oxygen radicals [1, 16]. Trimetazidine prevents ischemic ventricular fibrillation by maintaining homeostasis in cardiomyocytes. In trimetazidine-treated groups, cardiac enzymatic activities such as phosphorylase and ATPase increased significantly in ischemic areas in an animal experiment [1]. The protective effects of trimetazidine by increasing ventricular fibrillation threshold during coronary artery occlusion were consistent in both treated groups; however, no additional increase in the ventricular fibrillation threshold was found before occluding the coronary artery. Trimetazidine directly prevent cardiomyocyte vulnerability to ventricular fibrillation in ischemic conditions by balancing oxygen demand and supply [17].

Conclusion

Trimetazidine reduces oxidative damage after myocardial ischemia by reducing free radical oxidation products such as lipid peroxide and malondialdehyde in the mitochondria, thereby decreasing myocardial infarct size and ventricular fibrillation in animal studies. ■

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Psoriasis and risk of cardiovascular disease: case report and discussion

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Abstract

Psoriasis is a common inflammatory disease affecting 2% of the population. People who have severe psoriasis (requiring a systemic therapy) have a marked increase in cardiovascular disease. This could be due to an increased prevalence of traditional cardiovascular risk factors in people with psoriasis, the effect of chronic inflammation or a combination of both factors. Patients with severe disease should be risk assessed for cardiovascular disease and co-morbidities actively managed. ■ Heart Metab; 2013;60:30–33

Keywords: Psoriasis; inflammation; skin disease; cardiovascular disease; anti-TNF therapy.

Introduction

A 40-year-old lawyer has been followed in our severe psoriasis clinic since 2002. He first developed psoriasis in his twenties. He has a past medical history of mild psoriatic arthritis and hypercholesterolemia. He is an ex-smoker and drinks a moderate amount of alcohol. He is overweight (body mass index 26) but has no history of diabetes. He has a family history of ischemic heart disease. After 5 years of using topical skin treatments and phototherapy, in 2001 he required systemic therapy. He was treated with methotrexate, acitretin and cyclosporin between 2001 and 2007, when despite cyclosporin therapy, his psoriasis deteriorated.

The psoriasis area and severity index (PASI) is a validated and widely used disease severity scoring tool employed by the UK's National Institute of Health and Clincal Excellence (NICE) to guide suitability for systemic therapy. In 2007, his PASI score was 30.5 (range 0–72) and he therefore met NICE criteria for TNF antagonist therapy. He responded rapidly to 8-weekly infliximab infusions at 5 mg/kg (PASI 3 in March 2008) with complete disease control for 2 years. In August 2009 his psoriasis started to flare between treatments and his regime was altered to 6-weekly infusions.

In september 2009 he developed chest pain and shortness of breath during a trip to the hairdresser. He was hospitalized with an acute coronary syndrome, a troponin rise and an ischemic ECG. Slight chest pains during the infliximab infusion 7 days before the infarct triggered a collective decision to avoid further infusions, although the etiological relevance of infliximab in relation to the subsequent coronary event was never clear. Two months later his psoriasis flared. The initiation of bisoprolol and ramipril post infarction may have contributed to this; both drugs may exacerbate psoriasis [1]. During the same period he developed recurrent chest pain. In-stent restenosis was diagnosed and treated by a second angioplasty and stent within stent. A difficult year followed: his psoriasis was poorly controlled; stenoses in the RCA and left anterior descending arteries required stenting to alleviate chest pain and he also experienced two minor transient ischemic attacks. He underwent percutaneous coronary intervention of the RCA. Further episodes of chest pain in 2012 resulted in a coronary artery bypass grafting procedure.

In 2011, another systemic agent was sought to help control his severe psoriasis. Options were limited given his previous poor response to standard sys-

Abbreviations

CVD: cardiovascular disease; **ECG:** elctrocardiogram; **FAE:** fumeric acid esters; **IL:** interleukin; **JAMA:** Journal of the American Medical Association; **MACE:** major adverse cardiovascular event; **MI:** myocardial infarction; **RCA:** right coronary artery; **TNF:** tumour necrosis factor; **UK:** United Kingdom

temic therapy, and reluctance by both the patient and his cardiologist to try another TNF antagonist drug. He was therefore prescribed FAE, which induce apoptosis causing a reduction in peripheral CD4 and CD8 T cells and are used as first-line systemic therapy for chronic plaque psoriasis in Germany but remain unlicensed in the UK [2]. He achieved excellent disease control with FAE (PASI 2). In early 2013 this treatment was complicated by mild renal impairment with proteinuria presumed secondary to FAE therapy. A switch to ustekinumab, a monoclonal antibody (mAb) directed against the p40 unit shared by IL-12 and IL-23 (licensed for use in UK by NICE since 2009) for severe psoriasis is being considered but may be relatively contraindicated, in view of the possible link between p40 mAb (briakinumab, ustekinumab) and MACE [3].

Psoriasis

Psoriasis is a common inflammatory disease with environmental and genetic etiology, which affects approximately 2% of the population. The pathophysiology involves T-cell activation and release of cytokines including TNFα. Cutaneous inflammation combined with hyperproliferation of the epidermis results in erythematous, raised plaques with overlying scale. Nails are frequently involved and up to 30% of patients also have psoriatic arthritis [4, 5] (*Figure 1* [please note—the images used to illustrate this case are not of the patient described in the case report]).

Psoriasis and cardiovascular risk

A Swedish study published in 2004 attracted widespread interest when it reported that patients with psoriasis requiring hospital admission had a significantly increased risk of death from CVD compared to the general population [6]. This was followed by a large population-based study published in the JAMA, which identified psoriasis as a possible independent risk factor for MI [7]. A recent systematic review and meta-analysis designed to investigate incident CVD in people with psoriasis concluded that people who have severe disease (requiring systemic therapy or hospitalization) have a marked increase in CVD: the risk ratio relative to the general population for CVD mortality was 1.37 (95% CI 1.17–1.60) and 3.04 (95% CI 0.65–14.35) for MI. The relative risks of CVD were highest in the younger, severe disease population (3.10 [95% CI 1.98-4.86] for MI at 30 years) [8]. As a result of such research, psoriasis was cited as an independent risk factor for MI in the 2012 European guidelines on CVD prevention, which also recognize that the relative risk of MI is greatest in young patients and those with severe disease [5]. UK NICE guidelines published in October 2012 recommend that adults with severe psoriasis of any type should undergo a cardiovascular risk assessment at presentation using a validated risk assessment tool. They also recommend clinicians “offer a further assessment every 5 years or more frequently if indicated” [9].

The relationship between psoriasis and CVD is complex. Patients with psoriasis have an increased prevalence of coronary risk factors including metabolic syndrome [10, 11]. Psoriasis patients also tend to smoke more than the general population [12]. These factors may account for some if not all of the increased incidence of CVD seen in this group.

Inflammation has been recognized as an independent cardiovascular risk factor and there is an argument that a marker to reflect inflammation (such as highly sensitive C-reactive protein) should be added to cardiovascular risk scoring [13]. In an animal study using mice with psoriasiform dermatitis (KC-Tie2 mice) and an absence of comorbidities, aortic root inflammation was present in 33% of the affected KC-Tie2 group compared with 0% of controls (P = 0.04). After treatment of skin inflammation, the aortic root lesions resolved. The study showed that in murine models, skin inflammation alone promotes vascular inflammation and thrombosis [14]. The mechanisms linking psoriasis, metabolic syndrome and CVD have not yet been established in human subjects; one hypothesis invokes chronic T helper type 1 (Th1) inflammation [10]. A Th1-driven immune response that includes activated monocytes, macrophages and Th1 proinflammatory cytokines (including interferon and TNFα) is the hallmark of active psoriasis and also plays a role in metabolic syndrome and atherogenesis [4, 15].

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Anti-TNF therapy and CVD

If the relationship between psoriasis and CVD is causal – and currently this is not proved – then it can be hypothesized that treating psoriasis may abrogate the risk of CVD. With regard to older, oral systemic therapies for psoriasis (namely methotrexate, acitretin, cyclosporin), although it is accepted that certain drugs may increase individual cardiovascular risk factors (for example cyclosporin is linked to hypertension and dyslipidemia), the benefit of treating severe, active disease may decrease the overall incidence of MI [16–18].

Studies evaluating the effect of treatment with anti-TNFα therapies on the incidence of MI are ongoing. Published studies have shown mixed results; either lowering the risk or having no significant effect [18, 19]. There have been concerns that newer IL-12/23 agents (ustekinumab and briakinumab) may be associated with an increase in MACE. In 2011, after an elevated MACE rate was identified in a phase III briakinumab study, the sponsoring pharmaceutical company (Abbvie) withdrew the drug from further development. A JAMA meta-analysis [3] found no significant difference in the rate of MACE in patients with psoriasis treated with anti-TNFα/IL-12/23 agents compared to controls, although the study may have been underpowered and the authors advised clinicians to exercise caution in patients with identifiable cardiovascular risk factors when prescribing IL-12/23 agents. This year Papp et al [20] reviewed safety outcomes in patients treated with ustekinumab for up to 5 years and found no elevated risk of MACE. Although reassuring for clinicians, more comprehensive data from large, prospective registries are likely to give a clearer picture over the next 5–10 years.

Conclusion

Severe psoriasis is a risk factor for CVD. This could be due to an increased prevalence of traditional cardiovascular risk factors in people with psoriasis, the effect of chronic inflammation in patients with psoriasis or, more likely, a combination of both factors. Patients with severe disease should be risk-assessed for CVD and comorbidities should be actively managed. ■

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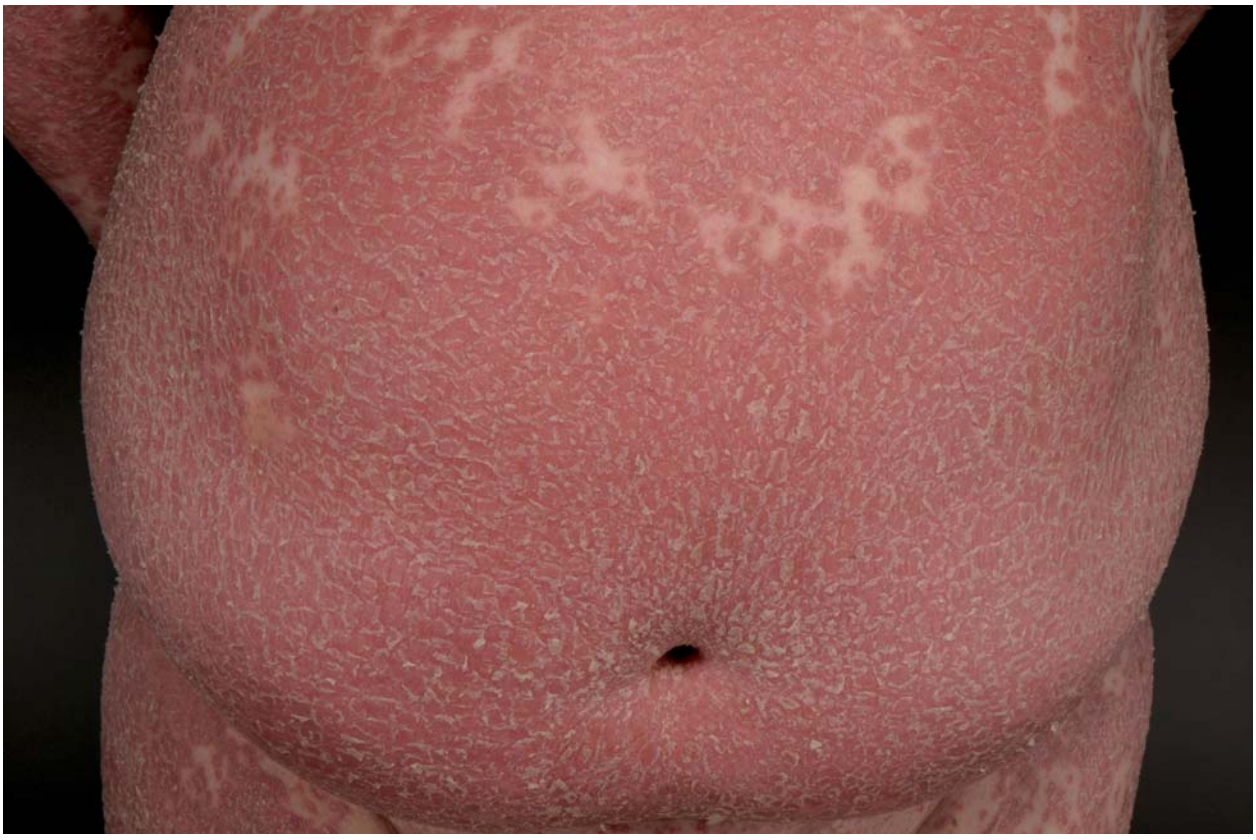

Fig. 1 *Patient with severe chronic plaque psoriasis.*

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