Trimetazidine effects on restoring endothelial function

Kyoung-Ha Park
Cardiovascular Division, Department of Internal Medicine, Hallym University Medical Center, Anyang, Korea

Correspondence: Dr Kyoung-Ha Park, Cardiovascular Division, Department of Internal Medicine, Hallym University Medical Center, 896, Pyeongchon-dong, Dongan-gu, Anyang-si, Gyeonggi-do, Korea
Tel: +82-31-380-3749; fax: +82-31-386-2269; email: pkhmd@naver.com

Abstract

Recent interest has focused on the antioxidant properties of trimetazidine and on its potentially beneficial effect on restoring endothelial function. Trimetazidine is the prototypical agent of a novel class of anti-anginal drug. In addition, trimetazidine is associated with improvements in the functional capacity of the myocardium, in the reduction of oxidative stress, and in the increase of nitric oxide expression, which enhances endothelial function. This article reviews recent laboratory and clinical trials that have assessed the role played by trimetazidine in restoring endothelial function.

Keywords: Endothelium; nitric oxide; oxidative stress; trimetazidine.

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The role of the endothelium

The endothelium is a thin layer of cells that lines the inner surface of blood vessels. This dynamic organ is largely responsible for the regulation of vascular smooth muscle tone; it also plays a key role in the regulation of thrombosis, inflammation, vascular permeability, and vascular smooth muscle growth [1]. In a study examining atherosclerosis in more than 3000 multi-ethnic subjects, endothelial function predicted future cardiovascular events even after adjustment for the conventional Framingham risk score [2]. Furthermore, in patients with coronary artery disease, endothelial function has been shown potentially to play a prognostic role in the secondary prevention of cardiovascular events [3]. Therefore, the endothelium plays a crucial role in regulating the process of atherosclerosis and in predicting a future cardiovascular event.

General effects of trimetazidine

Trimetazidine is the prototypical agent of a novel class of anti-anginal drug. By selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, it plays a crucial role in the β-oxidation of the myocardium [4]. Trimetazidine also has anti-ischemic effects through a number of mechanisms that include improvement of mitochondrial function, reduction of calcium overload, antioxidant effects, and preservation of high-energy phosphates [5, 6]. As a metabolic modulator, trimetazidine improves the functional capacity of the myocardium, which is associated with a reduction in oxidative stress, and it enhances endothelial function and decreases inflammation by reducing the rate of the inactivation of nitric oxide (NO) [7]. Therefore, trimetazidine improves the symptoms and the mechanical efficiency of dysfunctional myocardium, and it has

been shown to have a beneficial effect on the inflammatory profile and endothelial function in patients with ischemic cardiomyopathy [8].

The major effects of trimetazidine on vascular endothelium

Antioxidant effect

Previous studies have shown that trimetazidine has antioxidant properties that are strongly associated with beneficial effects that can improve endothelial dysfunction. In chronic heart failure, a reduction in cardiac antioxidant enzyme levels occurs and the plasma endothelin-1 level increases in parallel with the severity of left ventricular dysfunction [9]. Consequently, endothelial function is impaired because of the increased oxidative stress and altered vascular homeostasis. Fragasso and colleagues [10] reported that, in patients with ischemic cardiomyopathy, trimetazidine decreases plasma endothelin-1 levels and improves left ventricular dysfunction and vascular endothelial function. The authors found evidence that trimetazidine reduces the loss of intracellular potassium ion induced by oxygen free radicals in red cells as well as the membrane content of peroxidated lipids, which indicates the potent antioxidant activity of trimetazidine [11]. It is known that repeated administration of trimetazidine improves cardiac mitochondrial function, reduces the production of mitochondrial reactive oxygen species, and reduces oxidative damage in human and rat hearts [12, 13]. In addition, the treatment of trimetazidine attenuated reactive oxygen species production in both rat aortic smooth muscle cells and human umbilical endothelial cells. Therefore, it is conceivable that the antioxidant effects of trimetazidine played a role in reducing endothelial dysfunction [14].

Effects of trimetazidine on endothelial nitric oxide synthase

NO has long been known as an endothelium-derived relaxing factor. It is a vasodilator that regulates vascular tone, and it has been used as a nitrate donor for angina pectoris and heart failure. Furthermore, its powerful antioxidant, anti-inflammatory and antithrombotic actions are key factors for vascular endothelial protection and the anti-atherogenic process [15]. Di Napoli et al [16] reported that, in an isolated rat heart model with an ischemia–reperfusion injury, administration of trimetazidine reduces myocardial dysfunction and prevents vascular endothelial damage by increasing endothelial nitric oxide synthase (eNOS) expression [16]. The authors suggested the importance of preserving the anatomical and functional integrity of endothelium in the circulation system, and demonstrated that trimetazidine has a significant cytoprotective effect on vascular endothelial cells, partly preventing eNOS reduction. The action of trimetazidine on eNOS appears to be causally linked to the beneficial effects that trimetazidine has on ascular endothelial integrity and function.

Effects on the inflammatory profile

Although a clear mechanism has not been identified, recent studies have analyzed the impact of trimetazidine on markers of inflammation. There have been several data about how trimetazidine seems to decrease C-reactive protein (CRP) activity. In patients with ischemic dilated cardiomyopathy, the functional improvement of trimetazidine-treated patients was associated with a significant increase in left ventricular ejection fraction and improvement in ventricular remodeling. Moreover, the plasma concentration of CRP remained unchanged in the trimetazidine group, whereas a progressive increase in CRP levels was seen in the control group [17]. A recent study showed that in the diabetic rat, trimetazidine treatment reduced the serum concentrations of CRP in a dose-dependent manner [18]. These findings signify that trimetazidine plays a role in inflammatory response by contributing to the degree of vascular inflammation and atherosclerosis.

Direct and indirect effects of trimetazidine on the endothelium

Trimetazidine may have a direct effect on endothelial cells protecting the vascular endothelium from oxygen free radicals [18]. This action may be of particular importance in patients with diabetes and in patients who have medical conditions related to high oxidative stress in which low-density lipoprotein oxidation and hydrogen peroxide-induced DNA oxidative damage may directly injure the endothelial cells that cause abnormal gene expression and altered signal transduction. In addition, trimetazidine directly reduces the inactivation of NO through decreased production of lipid peroxidation [19, 20]. Trimetazidine's indirect effect on vascular endothelial function depends on its anti-ischemic properties and on the enhanced contractility of the dysfunctional myocardium, which both contribute to enhanced left ventricular myocardial function [21, 22].

Clinical and experimental evidence of trimetazidine's ability to improve endothelial function

Effects on endothelial function in chronic heart failure
Some studies have reported data demonstrating trimetazidine's ability to improve endothelium-dependent relaxation in patients with chronic heart failure [14]. Both experimental and clinical studies have found evidence that patients with greater oxidative stress with elevated oxygen free radicals usually have high plasma levels of malondialdehyde and lipid hydroperoxides, which are associated with severe endothelial dysfunction [23, 24]. Prasad et al [25] demonstrated that leukocyte-mediated production of oxygen-derived free radicals increases about 4-fold in patients with heart failure compared with control subjects. Moreover, Belardinelli et al [14] demonstrated that trimetazidine improves endothelium-dependent vasodilation, and this effect was correlated both with decreased plasma levels of malondialdehyde and hydroperoxides with various enhanced markers of cardiopulmonary functional exercise capacity. The improvement in conduit artery endothelium-dependent vasodilation after trimetazidine may be the consequence of both the direct effect and the indirect effect of trimetazidine on the endothelium.

Effects on damaged vascular endothelium

Although transradial catheterization for coronary angiography and percutaneous coronary intervention may induce functional and structural damage to the endothelial function of the radial artery (RA), the transradial procedure has been carried out in many centers. We recently reported that trimetazidine has favorable effects on the recovery of endothelial function of the RA after transradial catheterization [26]. In that study, 120 patients, who underwent transradial catheterization with either a 5 Fr or 6 Fr sheath, were randomly assigned to the trimetazidine group or the control group. Baseline, post-sheath injury (within 24 hours), and 10-week flow-mediated dilation (FMD) were performed in order to evaluate the endothelial function of the RA. In all cannulated RA, the post-sheath injury FMD were significantly lower than the baseline FMD. In the control group, the 10-week FMD was significantly lower than the baseline FMD, but no difference was found in the trimetazidine group (Figure 1). Therefore, the results suggested that trimetazidine therapy after transradial catheterization could improve the endothelial function of the cannulated RA.

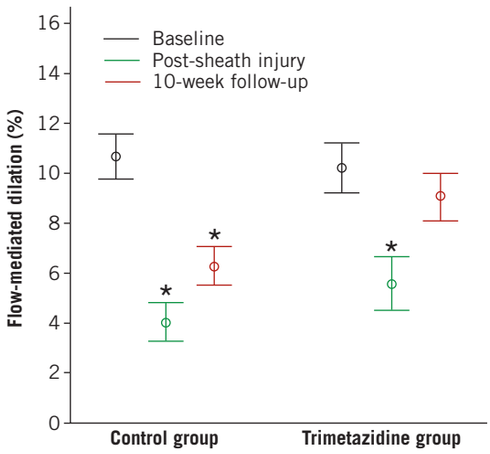

Fig. 1 *Study-wide changes in flow-mediated dilation of the cannulated radial artery for both groups. *P < 0.01 versus baseline. Reproduced with permission from Prasad et al [25].*

Effects on neointimal formation after vascular injury

In the field of percutaneous coronary intervention, restenosis and delayed re-endothelialization of the intervened vessel remains a critical issue. Inflammation, thrombosis, cellular proliferation, and extracellular matrix production contribute to neo-intimal hyperplasia and post-procedural luminal narrowing. The risk of restenosis is particularly high in patients with diabetes mellitus and may be partly associated with metabolic derangements that cause endothelial dysfunction [27]. Yoon et al [18] recently investigated the effects of trimetazidine on the occurrence of restenosis after vascular balloon injury of the carotid artery in both type 1 and type 2 rat models of diabetes. Four weeks of trimetazidine treatment resulted in a significant and dose-dependent reduction in the intimamedia ratio. This effect was accompanied by decreased proliferation of vascular smooth muscle cells and enhanced re-endothelialization of the carotid artery after balloon injury. In addition, trimetazidine therapy also increased the concentration of adiponectin and reduced the plasma levels of high sensitiviry CRP, tumor necrosis factor α and MCP-1, which means that the antioxidative and anti-inflammatory effects of trimetazidine preserved the function and structure of the carotid arterial endothelial cells after balloon injury.

Conclusions

It was well known that trimetazidine could play an important role in the treatment strategy for patients with

angina and heart failure. In addition, many experimental studies have shown that trimetazidine has the capacity to reduce oxidative stress while having a potentially beneficial effect on restoring endothelial function. However, the clinical data are still not sufficiently complete, and large randomized study and satisfactory solid data will be needed to verify the advantageous effect of trimetazidine on endothelial function. •

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