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# Endothelial Arginase: A New Target in Atherosclerosis

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Decreased endothelial nitric oxide (NO) bioavailability as it relates to endothelial dysfunction plays an important role in various cardiovascular disorders, including atherosclerosis. Recent research has provided evidence that endothelial dysfunction in atherosclerosis are not primarily caused by decreased endothelial NO synthase (eNOS) gene expression, but rather deregulation of eNOS enzymatic activity, which contributes to the increased oxidative stress in atherosclerosis. Among other mechanisms, the substrate L-arginine is an important limiting factor for NO production. Emerging evidence demonstrates that L-arginine is not only converted to NO via eNOS, but also metabolized to urea and L-ornithine via arginase in endothelial cells. Hence, arginase competes with eNOS for the substrate L-arginine, resulting in deceased NO production. There are an increasing number of studies showing that enhanced arginase gene expression and/or activity contribute to endothelial dysfunction in various cardiovascular disorders, including atherosclerosis. Thus, endothelial arginase may represent a new therapeutic target in atherosclerosis.

## Introduction

Atherosclerotic coronary artery disease remains the leading cause of death in industrialized countries, despite the remarkable progress being made toward understanding the mechanisms and therapeutic modalities in recent decades [1]. Pathogenesis of atherosclerosis is a complex process involving vasoconstriction, intimal thickening, and thrombus formation [1]. Dysfunctions of numerous cell types in the vascular wall (ie, endothelial and smooth muscle cells) and circulating blood (ie, platelets and white blood cells) all contribute to the disease process [1]. Research in recent decades provides substantial evidence that endothelial dysfunction as it relates to decreased bioavailability of endothelial nitric oxide (NO) plays an important role in atherogenesis [2,3].

Endothelium-derived NO is produced from the substrate L-arginine via endothelial NO synthase (eNOS), promotes vasodilation, and inhibits inflammation, platelet aggregation, and vascular smooth muscle cell (SMC) proliferation [4]. It is, therefore, not surprising that loss of endothelial NO function initiates and accelerates atherogenesis, as demonstrated by various experiments with animal models [5,6]. Although our understanding of biochemical regulation of endothelial NO bioactivity has remarkably advanced on various levels of eNOS gene expression—eNOS enzymatic activity to degradation of NO [7]—no single mechanism can fully explain endothelial dysfunction in atherosclerosis. Initial studies suggest that endothelial dysfunction in atherosclerosis is due to a decrease in eNOS gene expression [8]. Research in more recent years, however, provides evidence suggesting that reduced NO bioavailability, mainly due to a decrease in eNOS enzymatic activity rather than eNOS gene expression and accelerated inactivation of NO by oxidative stress, is the central mechanism of endothelial dysfunction in atherosclerosis [9]. This conclusion is supported by most studies of atherosclerotic animal models, showing an unchanged or even augmented protein level of eNOS in atherosclerotic arteries, despite the presence of endothelial dysfunction [10–12,13••]. Moreover, studies with human aortic and coronary arterial tissues obtained from autopsy or from transplant donors found only a significantly deceased eNOS gene expression in endothelial cells in advanced but not early atherosclerotic lesions [14,15]. Most recently, a study with human coronary atherectomy specimens showed a higher eNOS gene expression in patients with acute coronary syndromes than those with stable angina [16]. It is of particular importance to note that Ozaki et al. [17] recently showed acceleration of atherosclerotic lesion formation

in ApoE$^{-/-}$ mice overexpressing bovine eNOS transgene. Controversial results were, however, reported by van Haperen et al. [18] with the same experimental approach. The discrepancies in the results of the two studies are not clear. It has been speculated that the difference in severity of hypercholesterolemia and/or changes in blood pressure in animals between the two studies may explain the controversial results. Based on the outcomes of these, it can be asserted that endothelial dysfunction in atherosclerosis is not primarily caused by decreased eNOS gene expression. The studies also implicate that eNOS gene transfer into atherosclerotic arteries, which was initially proposed as a therapeutic approach to treat atherosclerosis, may not be generalized and should be carefully revisited. It is emerging that functional change in eNOS enzymatic activity rather than eNOS gene suppression plays an important role in endothelial dysfunction in atherosclerosis.

## Controversy of L-Arginine Supplemental Therapy in Atherosclerosis

The enzymatic activity of eNOS is affected by multiple factors, including post-translational modification associated with subcellular localization; the interacting proteins such as caveolin-1 and heat shock protein 90; and phosphorylation/dephosphorylation by protein kinases stimulated by hormonal agonists [7]. In addition, increase in endogenous eNOS inhibitor asymmetric dimethylarginine (ADMA), deficiency in co-factor tetrahydrobiopterin ($BH_4$), and deficiency in the substrate L-arginine have been proposed to cause so-called "uncoupling of eNOS" in atherosclerosis, a situation in which eNOS produces free radical superoxide anion instead of NO [17,19]. This mechanism may further contribute to inactivation of bioactive NO in atherosclerosis mediated by oxidative stress mediated by other enzymes such as NADPH-oxidase [19].

The bioavailability of L-arginine as a limiting factor for endothelial NO production was first recognized in the early 1990s. Several groups demonstrated that acute and chronic supplementation of L-arginine improves endothelial vasodilator responses in cholesterol fed animals and in patients with hypercholesterolemia and atherosclerosis [20–23]. Following these early studies, numerous studies with supplemental L-arginine therapy have been conducted in animal models and in humans; however, no consistent results can be achieved [24••]. In recent years, there has been an increasing number of studies showing either no effect or no sustained effects on endothelial function by L-arginine supplementation [6,25–30]. Harmful effects on atherosclerotic lesion formation in ApoE/iNOS double-knockout mice have been reported [31]. In this mouse model, the beneficial effect mediated by iNOS knockout on atherosclerotic lesion formation is eliminated with chronic L-arginine supplementation [31]. In line with this report, an increase in superoxide anion production was also demonstrated in atherosclerotic rabbit aortas treated with L-arginine [32]. The reason for the inconsistent results with L-arginine supplementation therapy is not clear. It might be due to the complex of the atherosclerotic disease process as well as the complex of biochemical metabolic pathways of the semi-amino acid L-arginine [33].

## Multiple Metabolic Pathways of L-Arginine

L-arginine, depending on cell types and tissues, undergoes multiple biochemical metabolisms and serves as precursor for a number of biologically active compounds involved in regulation of various cellular functions [33] (Fig. 1). As mentioned earlier, L-arginine is oxidized to NO and L-citrulline via eNOS in endothelial cells. Additionally, it is used for protein synthesis via arginyl t-RNA synthetase. L-arginine is also used for production of creatine via arginine:glycine amidinotransferase and guanidinoacetate N-methyltransferase, a pathway more restricted to the kidney and pancreas. Furthermore, L-arginine can be converted to L-agmatine via arginine decarboxylase (ADC) and to L-ornithine and urea via arginase, which is part of the urea cycle. Urea is then excreted through the kidney (Fig. 1). L-ornithine is further metabolized via ornithine decarboxylase (ODC) into polyamines that are important for cell proliferation [33]. L-ornithine can also be metabolized via ornithine aminotransferase (OAT) to L-proline, which is used for collagen production and deposition [33]. Hence, the production of polyamines and L-proline from L-arginine/L-ornithine may play a role in negative vascular remodeling [34] (Fig. 1). Among the metabolisms, there is recently increasing evidence suggesting a potential role of arginase in regulation of endothelial NO production by competing with eNOS for the substrate L-arginine. Increase in arginase activity has recently been demonstrated to play an important role in endothelial dysfunction under several pathophysiologic conditions, including atherosclerosis (see later).

## Role of Arginase in Endothelial Dysfunction

In mammals, there are two types of arginase, arginase I and II which are encoded by different genes [35]. Arginase I is a cytosolic enzyme, expressed most abundantly in the liver. The primary function of arginase I is ammonia detoxification. Arginase II is a mitochondrial enzyme, expressed primarily in the kidney or other extrahepatic tissues, including blood vessels [36]. The primary function of this type of enzyme is biosynthesis of polyamines and amino acids ornithine, proline, and glutamate [36]. Vascular endothelial and smooth muscle cells express both arginase I and II, but the relative level of the two types of enzyme seems different depending on species [13••,37–39]. In human endothelial cells, arginase II seems to be the predominant isoenzyme [13••,39]. The expression and activity of arginase II were found to be increased in human diabetic corpus cavernosum, and inhibition of the enzyme enhances NO-dependent relaxation of corpus cavernosum smooth muscle [40,41], suggesting a potential role for arginase II in negative regulation of NO production in diabetic erectile dysfunction. Similarly, arginase activity was also found to be higher in the aortas of type 1 and type 2 diabetic animal models

(Yang and Ming**,** Unpublished results). Our recent study demonstrates that in atherosclerotic aortas of ApoE$^{-/-}$ mice, arginase II was abundantly expressed, whereas arginase I was not detectable [13••]. Although the expression of arginase II was comparable between atherosclerotic and wild-type mice, the activity of the enzyme was increased in ApoE$^{-/-}$ animals, suggesting that increased enzymatic activity of arginase II plays a predominant role in atherosclerotic endothelial dysfunction.

It is quite surprising that L-arginine causes vasoconstriction in isolated mouse aortas, which is in contrast to the observation in rats and humans in which L-arginine evokes vascular relaxation by producing NO [13••]. Most interestingly, the contraction induced by L-arginine is much more pronounced in atherosclerotic ApoE$^{-/-}$ mice than in control animals. This contraction induced by L-arginine can be converted to a greater relaxation by the arginase inhibitor L-norvaline in atherosclerotic ApoE$^{-/-}$ mice than that in wild-type animals [13••]. The results demonstrate a dominant role of increased arginase activity in atherosclerotic endothelial dysfunction. The results also imply that in mouse aortas, particularly in the atherosclerotic ApoE$^{-/-}$ aortas, and perhaps also in humans depending on the stage of atherosclerosis, L-arginine can be metabolized by arginase to certain vasoconstrictive intermediate products. This hypothesis, if proven true, may explain the controversial results with L-arginine supplementation therapy. In line with the greater vascular relaxation induced by L-arginine in the presence of the arginase inhibitor, eNOS protein levels are also higher in atherosclerotic ApoE$^{-/-}$ aortas than in the wild-type animals [13••]. The results further support the concept that endothelial dysfunction in atherosclerosis is mainly due to decreased NO bioavailability rather than gene expression. A simple administration of L-arginine alone as anti-atherosclerotic therapy should not be generalized. Future research designed to target arginase specifically in the vasculature may provide a novel therapeutic approach to treat atherosclerosis and perhaps also other cardiovascular disorders.

Indeed, the role of arginase in endothelial dysfunction has been recently extended to other pathophysiologic conditions associated with vascular disorders in animal models such as aging [42,43], ischemia-reperfusion–induced endothelial dysfunction [44], and various types of hypertension [45,46,47••]. Most recently, the role of arginase in endothelial dysfunction has also been demonstrated in patients with primary pulmonary hypertension [48] and in patients with sickle cell disease [49••]. Importantly, arginase activity in blood plasma or red blood cells was found to be increased in patients with sickle cell disease, and is independently associated with pulmonary hypertension and mortality in these patients [49••].

## Regulation of Arginase Gene Expression and Activity in Endothelial Cells

Although there is evidence that arginase gene expression and/or activity is increased in various cardiovascular disorders, little information is available on the underlying regulatory mechanisms in the vasculature under the disease conditions, including atherosclerosis. Inflammatory cytokines have been shown to induce gene expression of arginase I and II in bovine endothelial cells, which is most likely mediated through transactivation of epidermal growth factor (EGF) receptors by the cytokines [50]. Our recent study provided the first evidence for the important role of RhoA/ROCK pathway in upregulation of arginase activity in human endothelial cells and in atherosclerotic blood vessels [13••]. We found that in human endothelial cells and atherosclerotic aortas of ApoE$^{-/-}$ mice, arginase I is not detectable by immunoblotting, whereas arginase II is abundantly expressed. Although the expression of arginase II is comparable in atherosclerotic and wild-type mice, the activity of the enzyme is significantly increased in ApoE$^{-/-}$ animals, suggesting that increased enzymatic activity of arginase II plays a predominant role in atherosclerotic endothelial dysfunction. The higher arginase activity in the atherosclerotic aorta is associated with higher RhoA protein level, suggesting a role for RhoA in upregulation of arginase activity. Indeed, in cultured human endothelial cells, arginase II enzymatic activity, but not protein expression, is enhanced by thrombin, a potent activator of RhoA/ROCK in endothelial cells, after 18 to 24 hours of stimulation. The enhanced arginase activity can be prevented by inhibitors of the RhoA/ROCK pathway. In line with this observation, adenovirus-mediated ectopic expression of a constitutively active mutant of RhoA or ROCK significantly enhanced arginase activity but not the gene expression in the cells. The results suggest that the Rho/ROCK pathway stimulates arginase II via regulating the enzymatic activity rather than gene expression. This regulatory model of arginase II in human endothelial cells is further supported by a study by Bachetti et al. [39], who showed that arginase activity but not gene expression in the cells was increased after 24 hours of stimulation with inflammatory cytokine mixture. The exact regulatory mechanisms of arginase activity in the cells and in atherosclerotic blood vessels remain an interesting topic for future research.

## Conclusions

Endothelial dysfunction in atherosclerosis is primarily caused by functional changes in eNOS enzymatic activity. Among other mechanisms, vascular endothelial arginase is emerging to play a substantial role in endothelial dysfunction under various pathophysiologic conditions, including atherosclerosis. Enhanced endothelial arginase activity competes with eNOS for the substrate L-arginine, resulting in decreased NO production. Various studies showed that inhibition of vascular arginase activity improves endothelial dysfunction under various pathologic conditions. These results suggest that targeting endothelial arginase may represent a new therapeutic approach for treatment of atherosclerosis and other cardiovascular disorders.

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Figure 1. The multiple metabolic pathways of L-arginine. ADC—arginine decarboxylase; eNOS—endothelial nitric oxide synthase; NO—nitric oxide; OAT— ornithine aminotransferase; ODC—ornithine decarboxylase; SMC—smooth muscle cell.