Asymmetric dimethylarginine, NO and collateral growth

Asimetrik dimetilarjinin, NO ve kollateral gelişim

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ABSTRACT

Atherosclerosis is a chronic inflammatory disease, which selectively involves the arteries in the vascular system. Atherosclerosis develops because of reactions occurring in vessel wall beginning with response to endothelial injury. Endothelial dysfunction is characterized with impairment and loss of monolayer cells covering the inside of the vessels, which is endothelium. Endothelial dysfunction is the first stage in atherosclerosis. Coronary angiogenesis and collateral growth are chronic adaptations to myocardial ischemia to restore coronary blood flow and salvage myocardium in the ischemic region. Nitric oxide (NO) which represents the status of endothelial health plays a major role in collateral vessel development. Asymmetric dimethylarginine (ADMA) which is endogenous inhibitor of NO synthesis may impair the effective coronary collateral vessel development. Increased plasma ADMA levels are related with poor coronary collateral development. ADMA may be responsible for the difference in coronary collateral vessel development among similar patients with coronary artery disease. Nitric oxide inhibitors have a determinative relation with endothelial cell functions which may be integral prerequisite in all steps of collateral development. The aim of this review is to evaluate the interrelations between ADMA and collateral growth. *(Anadolu Kardiyol Derg 2009; 9: 417-20)*

Key words: Nitric oxide, ADMA, endothelial dysfunction, collateral, atherosclerosis

ÖZET

Ateroskleroz vasküler sistemde seçici olarak arterleri tutan kronik bir hastalıktır. Ateroskleroz endotel hasarına yanıt olarak damar duvarında başlayan inflamatuvar reaksiyonlar sonucu gelişir. Endotel disfonksiyonu damar içini kaplayan tek katlı hücre tabakası olan endotelin bozulması ve kaybı ile karakterizedir. Endotel disfonksiyonu aterosklerozda ilk aşamadır. Koroner anjiyogenez ve kollateral gelişim iskemik alanda koroner kan akımını yeniden sağlamak ve miyokardiyumu kurtarmak için miyokardiyal iskemiye yönelik kronik adaptasyonlardır. Nitrik oksit (NO) endotelin sağlık durumunu yansıtır ve kollateral damar gelişiminde önemli bir rol oynar. Asimetrik dimetilarjinin (ADMA) NO sentezinin endojen inhibitörüdür ve etkin bir koroner kollateral damar gelişimini engelleyebilir. Plazma ADMA düzeylerinin artışı zayıf koroner kollateral gelişim ile ilişkilidir. Asimetrik dimetilarjinin koroner arter hastalığı olan benzer hastalar arasındaki koroner kollateral gelişimin farklı olmasından sorumlu olabilir. Nitrik oksit inhibitörleri endotel hücre fonksiyonları ile belirleyici bir ilişkiye sahiptir ve korunmuş endotel fonksiyonları kollateral gelişimin tüm aşamalarının vazgeçilmez bir ön şartı olabilir. Bu derlemenin amacı ADMA ve kollateral gelişim arasındaki karşılıklı ilişkiyi değerlendirmektir. *(Anadolu Kardiyol Derg 2009; 9: 417-20)*

Anahtar kelimeler: Nitrik oksit, ADMA, endotel disfonksiyonu, kollateral, ateroskleroz

Introduction

Atherosclerosis is a chronic inflammatory disease, which selectively involves the arteries in the vascular system. It is a continual process having complex interrelations with various causative factors. Atherosclerotic vascular complications are leading causes of morbidity and mortality in worldwide.

Endothelial dysfunction is characterized with impairment and loss of monolayer cells covering the inside of the vessels, which is endothelium. Endothelial dysfunction is the first stage in atherosclerosis. Atherosclerosis develops because of reactions occurring in vessel wall beginning with response to endothelial injury. These inflammatory reactions begin together with the increase in endothelial permeability caused by endothelial dysfunction, which represents the impaired balance between vascular damage and repair. The regenerative capacity of endothelium provides protection against atherosclerosis. Failure of the endothelial repair initiates atherosclerotic

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inflammation and lesion formation, so-called plaque, firstly in non-laminar flow stress points in vascular bed.

Coronary angiogenesis and collateral growth are chronic adaptations to myocardial ischemia to restore coronary blood flow and salvage myocardium in the ischemic region. Coronary collateral development has potential protective roles such as limited infract size, less ventricular aneurysm formation, improved ventricular function, fewer future cardiovascular events, and improved survival in patients with occlusive coronary lesions (1-5).

Nitric oxide (NO), which represents the status of endothelial health, plays a major role in collateral vessel development. Asymmetric dimethylarginine (ADMA) which is endogenous inhibitor of NO synthesis may impair the effective coronary collateral vessel development.

The aim of this review is to evaluate the interrelations between ADMA and collateral growth.

Endothelial function and nitric oxide

During the last half century, great advances in the treatment of acute and chronic forms of atherosclerosis have been obtained. These advances were provided by controlling of the offended risk factors for atherosclerosis and, by evidence based drugs and devices for its clinical manifestations. Together with these advances, today additional improvement cannot be provided on reached event reduction rates for treatment of stable coronary artery disease (CAD). This treatment resistance can be broken by discovery of new cells, cytokines, receptors, and regulators in vascular system.

The role of endothelium is beyond to be only a cell monolayer inside vessels. It was understood with recognition of the novel parameters that represent endothelium health status and independently predict the all-vascular events. However, like many mature cell lines, endothelial cells have a limited reparative ability, especially in pathological microenvironments produced by vascular risk factors.

Endothelium covers the inner surface of the vascular system and it is the most important structure for maintenance of normal vascular functions like control of vascular tonus, homeostasis and inflammation. Endothelial dysfunction causes problems in vasoactive, anticoagulant and anti-inflammatory effects of healthy endothelium, which leads to atherosclerosis in the vascular system. Nitric oxide is the most important molecule, which regulates the functions of endothelium and represents the health of endothelial function (6). It is synthesized from L-arginine by the help of nitric oxide synthase (NOS).

Asymmetric dimethylarginine, NO and endothelial dysfunction

Deficiency of NO is accepted as the key event in the beginning of atherosclerotic process. Asymmetric dimethylarginine is an end-product in protein catabolism. It is found to decrease nitric oxide bioavailability by interfering with its synthesis (7). Asymmetric dimethylarginine competes with L-arginine for the active site of endothelial NOS. It has been found to be associated with clinical conditions related with endothelial dysfunction like hypertension, diabetes mellitus and hyperlipidemia (8-10). Moreover, a strong relationship was shown between ADMA level and CAD (11-14). Valkonen et al. (11) observed a significant increase in the risk of major cardiovascular events in middle-aged nonsmoking men with higher plasma ADMA level. Plasma ADMA level was also shown to be higher in patients with a documented CAD compared to healthy control group in a multicenter case-control study (13). In a recent study, Meinitzer et al. (15) showed that plasma ADMA level predicts all-cause and cardiovascular mortality in patients with CAD. Moreover they observed a statistically nonsignificant trend to an increased risk of all cause mortality in controls without CAD but high level of plasma ADMA.

Collateral growth, NO and ADMA

Coronary angiogenesis and collateral growth are chronic adaptations to myocardial ischemia to restore coronary blood flow and salvage myocardium in the ischemic region. Coronary collateral development has potential protective benefits such as limited infract size, less ventricular aneurysm formation, improved ventricular function, fewer future cardiovascular events, and improved survival in patients with occlusive coronary lesions (1-5). Several contributing factors have been reported in relation to collateral development. The severity of coronary artery stenosis and the duration of myocardial ischemic symptoms have been found in association with good collateral formation (16-18). Patients with diabetes, hypercholesterolemia, and hypertension have less ability to create collateral vessels (16-19).

In our opinion, four stages are very important in the collateral development. First stage is the first response of any tissue to ischemia; second stage is the target tissue and cells for collateral development; third stage is the active and increased functional cells by the stimulant cytokines, and last stage is the capability of cell homing to ischemic tissue. Collateral growth is a multistage process and all of the above stages can be disturbed by various risk factors, which can harm the integrity of arteriogenesis. Besides, there can be genetically defective background in patients with poor collateral growth, which prevent good collateral growth at any stage of arteriogenesis.

In a recent study related to collateral development, various cytokines were studied but insufficient results were obtained (20). Heterogeneity in collateral formation despite similar degrees of coronary obstruction may be related to several factors such as different effects of inflammatory cells, the capability of cell homing factors in the ischemic tissue and levels of both cytokines and chemokines related with ischemic tissue. The quantity and quality of functional cells may be critical in the development of collaterals. Besides, these four stages may be operative by undefined mechanisms such as other cells, cytokines and receptors that contribute to inflammation process.

Growth factors like vascular endothelial growth factor (VEGF) are thought to play the major role in collateral development through the activation of tyrosine kinase receptors leading to NO release (21, 22). So, endothelial dysfunction characterized by NO deficiency would decrease collateral development (23). However, the role of ADMA in this inhibition of collateral development is less known.

If the importance of healthy endothelium for coronary collateral vessel development is considered, ADMA level may affect the collateral development. Heterogeneity in collateral formation despite similar degrees of coronary obstruction can be related to different effects of endothelial cells and their functions, on the development of collaterals.

In prior study, we aimed to interrogate whether coronary collateral development has any association with ADMA levels, which play an important role in development of endothelial dysfunction. We found that plasma ADMA level was higher in patients with poor coronary collateral development (24). Moreover, we also observed that L-arginine/ADMA ratio was decreased in patients with lower degree of coronary collateral development. Asymmetric dimethylarginine may be an important mediator for the mechanisms, which limit collateral formation.

The collateral vessels can serve an important function in patients with significant obstruction of a coronary artery by providing an extra blood supply to the ischemic area (2). It is shown that collateral vessel development shows a good correlation with the severity of myocardial ischemia (18). However, we do not observe the same degree of collateral vessel development in every patient with significant ischemia. Identification of the mechanisms affecting collateral formation may help to build up new strategies to enhance collateral formation.

Previous studies showed that there is a negative relationship between collateral development and cardiovascular risk factors related with endothelial dysfunction such as age, diabetes mellitus, metabolic syndrome, and obesity (25-27). Deficiency of NO is accepted as the main problem in endothelial dysfunction.

In several studies, NO was found to be crucial for angiogenesis. Endothelial NOS activity was closely related with the angiogenic capability in animal models (28, 29). Furthermore, the activity of VEGF, which is accepted to be one of the most important mediators in collateral formation is shown to be enhanced by NO (29). The primary collateral circuit formed by angiogenesis is vasoresponsive to NO (30). Nitric oxide can induce vasodilatation of this collateral circuit and lead to an increase in collateral dependent flow. Recently, endothelial NOS gene Glu298Asp polymorphism was also found to be related with poor coronary collateral development, indicating the importance of NO in collateral formation (31). Therefore, factors interfering with NO activity would lead to a reduction in effective collateral development.

Asymmetric dimethylarginine stands at the key point in one of the most important mechanisms for NO inhibition (7). It is an endogenous competitive inhibitor of NO synthesis. Although it is not demonstrated the exact mechanism of the relationship between ADMA and poor collateral development, increased plasma ADMA level may impair coronary collateral development by decreasing NO synthesis. In a recent study by Jacobi et al. (32), decreased tissue and plasma ADMA levels were found to be related with enhanced angiogenesis in transgenic mice that over-expresses the human isoform of the enzyme responsible from the degradation of ADMA, dimethylarginine-dimethylaminohydrolase. This finding supports that increased ADMA level may interfere with angiogenesis.

Inhibition of nitric oxide synthesis may not be the only mechanism that is responsible for poor coronary collateral development in presence of higher plasma ADMA levels. Increased ADMA level may also upregulate angiotensin converting enzyme and lead further activation of renin-angiotensin-aldosterone system (33). Resultant increase in vasoconstrictor molecules may limit the formation of structural development of effective collateral system and cause further decrease in NO synthesis. Administration of drugs such as angiotensin converting enzyme inhibitors may help to improve collateral formation.

Asymmetric dimethylarginine competes with L-arginine for the active site of endothelial nitric oxide synthase (7). So the relative amount of L-arginine to ADMA determines the degree of NO inhibition and may affect coronary collateral development. For this reason, there is stronger correlation between coronary collateral vessel development and L-arginine/ADMA ratio than being with ADMA (24). While this association suggests a critical role for NO on collateral development, it also supports the integral regulator function of endothelium in this process. In our opinion, there is probably a defect in ischemia-induced cytokine generation of endothelium in patients with poor collateral growth and this defect is potentiated by ADMA.

Conclusion

Increased plasma ADMA levels are related with poor coronary collateral development. ADMA may be responsible for the difference in coronary collateral vessel development among similar patients with coronary artery disease. Nitric oxide inhibitors have a determinative relation with endothelial cell functions, which may be integral prerequisite in all steps of collateral development. Asymmetric dimethylarginine may be one of the factors, which determine the degree of collateral development and may provide a new target for the treatment strategies to enhance coronary collateral vessel development. Studies with larger study populations are required to clarify this relationship between ADMA and coronary collateral development.

Conflicts of Interest: There is no conflict of interest related to the submitted manuscript.

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