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Atherosclerosis and NO (L-Arginine)

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Atherosclerosis is a chronic inflammatory process in the intima layer of the arteries, which disturbs the endothelium-dependent regulation of the vascular tone by the labile radical nitric oxide (NO) formed by the endothelial nitric oxide synthase (eNOS). This defect predisposes to coronary vasospasm and cardiac ischaemia, with anginal pain as the typical clinical manifestation. It is now appreciated that endothelial dysfunction is an early event in the process of atherogenesis and that it may also involve the microcirculation, in which atherosclerotic lesions can not be developed. On the other hand, the inflammatory environment in atherosclerotic plaques may result in the expression of the NO synthase (iNOS) isozyme. Whether the dysfunction in endothelial NO production is causal to, or the result of, atherosclerotic lesion formation is still highly debated.

Endothelium damage induced by atherosclerosis leads to the reduction in bioactivity of endothelial NO synthase (eNOS) with subsequent impaired release of NO together by increased generation of reactive oxygen species (ROS) with subsequent cascade of oxidation-sensitive mechanisms in the arterial wall. Many commonly used vasculoprotective agents have their therapeutic actions through the production of NO. L-Arginine, the main substance of NO, has demonstrated beneficial effects in atherosclerosis and disturbed shear stress, which has one of the main roles of vessel inflammation, when it is in high levels.

Intravenous infusions of l-arginine

Arginine and risk factors for atherosclerosis The impact of l-arginine in atherogenesis and its ability to prevent the consequences of atherosclerosis risk factors on endothelium have been studied extensively during the last few years by researchers using inrtra-arterial, intravenous or intracoronary infusions of l-arginine. Or by using as a powder food supplement.

Hypercholesterolemia has been shown that intracoronary infusion of l-arginine restores endothelium-dependent vasodilation in the coronary microcirculation of hypercholesterolemic patients, but had no effects on epicardial arteries. It has been found that the dilation of proximal and distal coronary segments, in response to l-arginine at a concentration of 50 mmol/l, was greater in patients with serum cholesterol levels less or equal to 200 mg/dl than in patients with cholesterol levels greater than 200 mg/dl [1].

There is a study that hypercholesterolemic patients needed an infusion of at least 150 mmol/l l-arginine to achieve the same vasodilatory effect, showing that cholesterol levels may affect the response of epicardial arteries to l-arginine.

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In another study, using intravenous infusions, l-arginine increased the forearm dilation in hypercholesterolemic subjects. Moreover, intra-arterial infusion of this amino acid increased the vasodilatory response in atherosclerotic patients. However, acute existance of l-arginine inhibited platelet reducing the clot formation.

Furthermore consuming l-Arginine by powder form as a food supplement, reversed the abnormal myocardial blood flow response to cold press or test in smokers. Additionally, intravenous infusion of l-arginine improved endothelial function of the arteries in general in healthy smokers (not smokers with CVD or CAD). However, there is not significant difference in the vasomotor effect of intracoronary infused l- arginine between smokers and non-smokers, possibly due to the small number of patients.

Some clinical studies using intracoronary infusions might offer important information on the pathophysiologic aspects of l-arginine administration, Hypertension as the effect of l-arginine on endothelial function in hypertensive patients has also been studied and have been announced scientifically.

However, this dilation was markedly impaired in hypertensive patients with renal insuficiency compared with normal control subjects and patients with essential hypertension who had normal renal function, indicating that l-arginine plays a role in blood pressure control by dilating renal vasculature. Beyond the vasodilatory effects of l-arginine, this amino acid also inhibits angiotensin-converting enzyme, leading to further decrease in blood pressure.

L-arginine infusion decreased blood pressure in hypertensive patients without any significant effect in patients with a history of accelerated-malignant hypertension. This might be a result of the different underlying mechanisms of endothelial dysfunction observed between the two categories of hypertensive patients, since in hypertensive patients with accelerated malignant hypertension severe impairment of the l-arginine/NO pathway is present.

Intra-arterial infusion of l-arginine failed to improve endothelial function in hypertensive patients. It has been shown that l-arginine improved the response to acetylcholine in offspring of essential hypertensive patients where endothelial dysfunction was observed. The different pathophysiologic mechanisms of systemic hypertension might be the reason for the variability observed. l-Arginine might be effective in some types of hypertension while in other types it might be ineffective. Furthermore, It may indicate that the most important mechanism by which chronic treatment with l-arginine may affect arterial hypertension is the decrease of renal vascular resistance, beyond its peripheral vasodilatory effect. Renal hypertension has an ultimate affection to the vascular hypertension and to CHF (Chronic Heart Failure).

Diabetes Intravenous infusions of l-arginine have been used in non-insulin-dependent diabetic patients with angiographically normal coronary arteries and no other risk factors, showing no improvement of coronary artery responses to physiological stimuli. On the other hand, it has also been shown that an intravenous bolus of l- arginine up to 5 g reduced mean blood pressure and decreased platelet aggregation in patients with insulin-dependent diabetes mellitus. Furthermore, intravenous infusion of l-arginine in newly diagnosed non-insulin-dependent diabetic patients reduced blood pressure and improved hemodynamic function.

In diabetic patients, the endothelial dysfunction is not based only on eNOS-substrate deficiency but on multiple mechanisms such as increased oxidative stress, decreased antioxidant status, decreased eNOS activation and others. Therefore, peripheral or coronary endothelial function may not be consistently improved by l-arginine in these patients since its antioxidant ability is rather limited at the dosages usually used. However, l-arginine remains effective as an agent for the treatment of arterial hypertension in diabetic patients by improving endothelial function, reducing arterial pressure and decreasing platelet aggregation.

In conclusion, a possible role of l-arginine in modifying the effect of atherosclerosis risk factors on vascular endothelium has been shown in studies using parenteral

administration. l-Arginine seems to be beneficial in hypercholesterolemic and hypertensive patients as well as smokers.

Its role in diabetes mellitus remains controversial since its effects on endothelial function are variable, despite the possible positive effects on arterial hypertension and platelet aggregation in these patients [2-14].

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