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## ABSTRACT OF ARTERY

**HOMOCYSTEINE, LARGE ARTERIES AND CARDIOVASCULAR RISK**

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The relationship of homocysteine (Hcy) with vascular disease has been known since 1969 when severe coronary atherosclerosis was found at autopsy in children suffering with inborn defects of Hcy metabolism. There are several hypotheses of how Hcy can be etiologic factor causing cardiovascular disease. (1) Hcy is toxic for endothelium and its high level results in endothelial dysfunction through decreased availability of nitric oxide (NO). One mechanism is the increased production of peroxide and superoxide anions and consequent accelerated oxidative degradation of nitric oxide. Furthermore, Hcy causes increase of asymmetric dimethylarginine which acts as competitive inhibitor of NO synthase. Endothelial dysfunction was found in subjects with severe hyperhomocysteinemia, mainly by the presence of impaired endothelium-dependent vasodilation of coronary and forearm arteries; the effect of mild Hcy increase is, however, less evident. (2) Besides endothelium, Hcy influences the metabolism of connective tissue in vascular media. It has been shown in experimental studies that Hcy increases collagen synthesis in vascular smooth muscle cell culture and decreases elastin content in elastic-type arteries through accelerated elastolysis. (3) High Hcy levels impair hemocoagulation by several mechanisms, thus increasing the probability of thrombotic events.

The "homocysteine theory of atherosclerosis" was neglected by clinicians and cardiovascular epidemiologists for a long time. The first metanalysis of larger prospective studies was published in 1995 (Boushey et al., JAMA); it revealed that a 5  $\mu\text{mol/l}$  increase in Hcy levels was associated with a 60% increase of coronary artery disease risk in men and an 80% increase in women.

There are several studies on Hcy and large artery properties. Two cross-sectional studies on the relationships between Hcy levels and aortic stiffness, measured by pulse wave velocity, were published (Bortolotto et al., Hypertension 1999, Mayer, Filipovský et al., J Human Hypertension 2006). Aortic stiffness was found to be independently associated with Hcy in both. Other smaller studies, however, showed no relationship of homocysteine to either aortic or carotid stiffness. When methionine loading was used to increase acutely Hcy level in healthy volunteers, the increase in arterial

stiffness was induced in two studies, but no change was observed in one study. In another study of patients with end-stage renal disease (Blacher et al., Arterioscler Thromb Vasc Biol 1998), Hcy was associated with lower-limb, but not upper-limb or aortic stiffness. Thus, the data about the effect of Hcy on large arteries are conflicting.

The effect of Hcy lowering in patients with severe hyperhomocysteinemia due to cystathione beta-synthase deficiency was shown by a landmark study by Yap et al. (Arterioscler Thromb Vasc Biol 2001). Therapy based on vitamine B<sub>6</sub> was given to 158 subjects for a mean follow-up of 17.9 years. The group was compared with historical controls from a study of 629 untreated patients with the same inborn defect. There were 17 vascular events in the treated subjects, while without treatment, 112 events would have been expected; the relative risk was 0.09.

In patients with mild Hcy elevation, folate administration is the most effective. A low dose of 0.5 mg/day has the same effect as higher doses (5 mg/day); Hcy level is reduced on average by 25%. Several large interventional studies with hard end-points are ongoing. The data of VISP trial (Vitamin Intervention for Stroke Prevention; Toole et al., JAMA 2004) showed no difference in composite cardiovascular endpoint between high- and low-dose multivitamine B treatment in nearly 4000 post-stroke patients during an average two-year follow-up. Similarly, the HOPE-2 trial, where subjects with established cardiovascular disease or diabetes were randomized, regardless of their Hcy level at entry, to either Hcy-lowering therapy or placebo and followed for five years, did not show any positive or negative cardiovascular effect. The potential treatment effect might be, however, diluted due to very common folate and vitamine B supplementation in general population.

It can be concluded that the extremely high homocystein level as seen in some inborn diseases is a risk factor for cardiovascular disease, but this causal relationship is less clear for subjects with mild hyperhomocysteinemia. Up to now, no effect on hard endpoints in these subjects was shown. This does not rule out, however, that the effect would be seen in more tightly defined patient samples, especially according to baseline Hcy level and at high cardiovascular risk. As for large arteries, Hcy acts on endothelial function, smooth muscle cell function and matrix composition; its effect may vary in different parts of vascular tree. It remains to be elucidated whether these effects are of clinical relevance.