S-ADENOSYLHOMOCYSTEINE MEDIATES HOMOCYSTEINE ATHEROGENICITY BY SUPPRESSING THE FGF2-PROSURVIVAL PATHWAY IN ACUTE MYOCARDIAL INFARCTION

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Background: Emerging data have suggested that S-adenosylhomocysteine (SAH) might be a better indicator of vascular pathogenesis than homocysteine. In this study, we investigated the clinical significance and mechanistic role of SAH in acute myocardial infarction.

Methods: Blood samples were collected from adult subjects with acute ST elevation myocardial infarction (n=10) or healthy controls (n=10). Plasma SAH levels were quantitated by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). A cell culture system was established to access the relative importance of SAH over homocysteine using human coronary artery endothelial cells (ECs).

Results: In ten patients with ST-elevation myocardial infarction, the plasma SAH levels were significantly increased compared to healthy controls (61±11 nM vs. 21±5 nM; P<0.01). In contrast, their plasma homocysteine concentrations were similar (10.5±1.1 uM vs. 13.5±1.2 uM). In human coronary artery ECs, homocysteine alone did not affect EC survival up to 500 uM; however, as low as 50 uM homocysteine was sufficient to impair cell viability when intracellular SAH was simultaneously elevated. Co-incubated with adenosine/EHNA, homocysteine (25-500 uM) dose-dependently increased intracellular SAH, TUNEL-positive apoptotic cell death, and downregulation of fibroblast growth factor 2 through promoter DNA methylation. The EC adverse effects could be eliminated when intracellular SAH levels were lowered by removing adenosine/EHNA from culture medium, which was in agreement with clinical resolution of myocardial infarction six months later when plasma SAH in these patients markedly decreased (21±4 nM; from 61±11 nM).

Conclusions: Our data have demonstrated an indispensable role of SAH in homocysteine-mediated EC injury. The elevation of plasma SAH but not homocysteine in acute myocardial infarction further implicates SAH as a better indicator of vascular diseases than homocysteine. Large-scale epidemiologic and prospective investigations are needed to determine whether SAH can be identified as a new therapeutic target.