

Heterozygous PAI-1 Deficiency's Role in Pathological Aging in the Human Cardiovascular System

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Background and Objective: Plasminogen activator inhibitor (PAI-1) is a member of the fibrinolytic system and a marker and a mediator of cellular senescence. Experimental evidence in humans suggests that higher levels of PAI-1 are associated with increased pathological aging in several major organ systems of the human body. To better understand the role of PAI-1 in humans, specifically in the cardiovascular system, we studied the effects of a loss-of-function mutation in *SERPINE1*, the gene encoding PAI-1, in an Old Order Amish community in Berne, Indiana. Overall, carriers of the null *SERPINE1* variant had greater leukocyte telomere lengths, lower fasting insulin levels, and less prevalent diabetes mellitus. To further the conclusions previously published, our goal is to continue to analyze data collected alongside demographic data to determine if there is a link between PAI-1 deficiency and protection against aging-related changes in the human cardiovascular system. We hypothesized that the differences between the cardiovascular endpoints between carriers and non-carriers will be most significant in older groups.

Methods: Participants included 177 members of the community, 43 of which were carriers for the *SERPINE1* mutation. To test our hypothesis, we divided participants into tertiles and compared the results of selected cardiovascular parameters of those with and without the mutation in each tertile.

Results: Our analysis revealed a statistically significant difference in brachial pulse pressures between carriers of the null mutation and normal individuals in the third tertile, corresponding to individuals ages 55 to 82. Those heterozygous for the mutation in this age group had a lower brachial pulse pressure, suggesting there are protective effects of PAI-1 haploinsufficiency against endothelial senescence as people age.

Potential Impact: By identifying the age group with the most pronounced effects of PAI-1 deficiency, we can further investigate the means by which these results manifest in humans and better understand where in the aging process they are most significant.