

SOCIETY OF GERIATRIC CARDIOLOGY-ASP-
AMERICAN HEART ASSOCIATION
CAREER DEVELOPMENT AWARD IN GERIATRIC CARDIOLOGY



AWARD RECIPIENT

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PROJECT

"METABOLIC SYNDROME AND ENDOTHELIAL T-PA RELEASE IN OLDER ADULTS"

MENTORSHIP TEAM

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In the United States, cardiovascular diseases are the leading cause of death and disability. Over 80% of all cardiovascular events occur in adults over 65 years of age. A number of studies have found that adults with metabolic syndrome are at increased risk for atherothrombotic cardiovascular disease. Indeed, while the predictive power of many traditional cardiovascular risk factors fades with increasing age, a persistent increase in risk of cardiovascular events remains in adults over 70 years of age with metabolic syndrome. As the US population becomes older and more obese the incidence and prevalence of metabolic syndrome will increase. More importantly the atherothrombotic complications associated with this syndrome will increase substantially.

Endothelial health, specifically the ability of the vascular endothelium to release tissue-type plasminogen activator (t-PA), plays a crucial role in the prevention of atherothrombotic events. Impairment of normal endothelial activity, termed endothelial dysfunction, occurs in responses to numerous blood-borne insults. The deleterious effects of traditional and novel cardiovascular risk factors are mediated largely through the endothelium. One proposed unifying mechanism explaining how disparate risk factors lead to atherosclerosis is oxidative stress. Oxidative stress leads to endothelial dysfunction which in turn induces vascular inflammation that may further promote oxidative stress in a feed-forward fashion, ultimately leading to atherosclerosis. Metabolic syndrome is associated with lower endogenous antioxidant levels, increased oxidative stress and endothelial dysfunction, demonstrated by impairment in vasodilation. In addition to endothelial vasodilation, *in vitro* studies suggest oxidative stress may impair endothelial cell fibrinolysis. Currently it is unknown whether oxidative stress has a direct modulatory influence on the

capacity of the vascular endothelium to release t-PA in older adults with metabolic syndrome. If so, this identifies an avenue for therapeutic intervention (i.e., antioxidant therapy) to reduce the thrombotic tendency associated with metabolic syndrome.

The capacity of the endothelium to release t-PA is a primary mechanism underlying endogenous fibrinolytic activity and a novel target for primary and secondary prevention of atherothrombosis. Thus, the goal of this study is to identify whether endothelial fibrinolytic capacity is impaired in this growing population at elevated risk of atherothrombotic events. Furthermore, the project will determine whether this impairment is secondary to oxidative stress and associated with subclinical inflammation. The expected results would provide the experimental rationale for studies to investigate the effects of antioxidant therapy, such as oral vitamin C supplementation on vascular endothelial function in older adults with the metabolic syndrome. The ultimate goal is the use of a safe and inexpensive therapy for the primary prevention of cardiovascular events in a population with a documented increased risk of cardiovascular disease.

The Society of Geriatric Cardiology-ASP-American Heart Association Career Development Award in Geriatric Cardiology will provide support to advance our understanding of mechanisms of cardiovascular disease and possible therapies for disease prevention. In addition, the award will provide the mechanism to improve communication between the Divisions of Cardiology and Geriatrics at the University of Colorado and increase education of both faculty and fellows within these divisions. Greater communication and education will facilitate the prevention, diagnosis, and treatment of cardiovascular disease in older adults.