# Contribution of Perivascular Adipose Tissue to Coronary Vascular Dysfunction

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## Abstract:

The epidemic of obesity and associated cardiovascular complications continues to grow at an alarming rate. Currently, obesity is thought to initiate a state of chronic inflammation, which if unresolved potentially causes cardiovascular dysfunction and disease. Although poorly understood, release of inflammatory mediators and other cytokines from adipose tissue (adipocytokines) has been proposed to be the molecular link between obesity and coronary artery disease. Furthermore, the anatomic location of adipose has been increasingly recognized as a potential contributor to vascular disease. Importantly, the development of coronary atherosclerosis, a key component of heart disease, is typically found in segments of coronary arteries surrounded by perivascular adipose tissue. Accordingly, the goal of this project was to determine how perivascular adipose tissue affects coronary artery function and elucidate the critical mechanisms involved. Initial studies assessing arterial function were conducted with and

without perivascular adipose tissue. Preliminary results demonstrated that factors released by perivascular adipose tissue effectively impaired coronary endothelial function both in vitro and in vivo. This observation was determined to be caused by direct inhibition of nitric oxide synthase (NOS), a critical enzyme for the production nitric oxide. Attenuation of endothelium-dependent vasodilation was independent of changes in superoxide production, smooth muscle response, or peroxide-mediated vasodilation. Additional studies revealed that perivascular adipose-induced impairment of NOS was due to increased inhibitory regulation by the β isoform of protein kinase C (PKC-β). Specifically, perivascular adipose-derived factors caused site specific phosphorylation of nitric oxide synthase at Thr-495. Additional experiments investigated how perivascular adipose-derived factors contributed to coronary artery disease in an animal model of obesity. Results from these studies indicated that perivascular adipose-derived leptin markedly exacerbated underlying endothelial dysfunction, and significantly contributed to coronary endothelial dysfunction through a PKC-β dependent mechanism. Findings from this project confirm epicardial perivascular adipose tissue as a local source of harmful adipocytokines. In addition, perivascular adipose-derived leptin was demonstrated to be a critical mediator of coronary vascular dysfunction in obesity. Together, the results strongly suggest that perivascular adipose tissue is a key contributor to coronary artery disease in obesity.

## Description:

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