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Exercise Reverses Metabolic Syndrome Perivascular Adipose Tissue Impairment of Aortic Relaxation

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Thoracic aorta perivascular adipose tissue (PVAT) mediates aortic function through paracrine signaling. In health these factors are predominately anti-inflammatory and aide in proper vascular function. Our previous data shows PVAT is "brown-like" expressing high levels of Uncoupling Protein-1 (UCP-1), however in the metabolic syndrome (MetS) the PVAT loses the expression of UCP-1 shifting to a white-like phenotype. This shift is accompanied with increased oxidative stress and expression of pro-inflammatory cytokines, which can impair aortic endothelial nitric oxide (NO) production and alter extracellular matrix composition. The objective of the study was to determine the therapeutic efficacy of aerobic exercise in an animal model of MetS (obese zucker rats: OZR) specifically on PVAT mediated NO production, aortic relaxation, and aortic stiffness.

OZR PVAT expression of UCP-1 decreased 100- fold accompanied by a greater than 70 fold increase in both TNFα and IL-6. This inflammatory secretion profile further diminished endothelial dependent relaxation of the aorta by 15%. Using the DHE assay, we found a >100% increased superoxide production in the PVAT ($p<0.01$). Exercise is known to have anti-oxidant and anti-inflammatory benefits but little is know of this impact on PVAT. We previously found improved UCP-1, SOD-1, TNFα and IL-6 gene expression in OZRs following 8 weeks of treadmill training. Exercise improved aortic endothelial relaxation 10% ($p<0.01$), additionally PVAT augmented relaxation 10% ($p<0.01$) instead of impairing. This may be the result of diminished superoxide production (DHE fluorescence $p<0.05$) in the PVAT restoring a healthy pro/anti inflammatory balance. Exercise also reduced constricting responses to phenylephrine with and without PVAT. Similarly in the lean rats (LZR) exercise training increased UCP-1 expression along with SOD-1 with marginal increase in aortic relaxation and PVAT mediated aortic relaxation. Exercise also augmented the anti-contractile effects of PVAT.

Structurally MetS causes increase deposition of collagen with fragmentation of elastin increasing the aorta's resistance to deformation. OZR have increase elastin modulus compared to LZR (561 vs. 304 N, $p<0.01$) showing increased stiffness, which is completely reversed by exercise training (561 vs. 337 N, $p<0.01$) in OZR. Previous PVAT gene expression showed increase in MMP9 a marker that correlate strongly with aortic stiffness and similar to the elastin modulus exercise training completely returns expression level to that of LZRs. This establishes a correlative relationship between PVAT expression of MMPs and mechanical aortic stiffness.

In summary MetS PVAT mediates increases in both functional (endothelial function) and structural stiffness (matrix remodeling). 8 weeks of treadmill training in OZRs promotes beneficial gene expression in the PVAT leading to reduced superoxide production, decreased pro-inflammatory cytokines, and retention of aortic elastic properties.

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