

**VASCULAR ACTIONS OF INSULIN IN CARDIOMETABOLIC DISEASE:  
EFFECTS OF METFORMIN, PHYSICAL ACTIVITY,  
AND INTRINSIC AEROBIC FITNESS**

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**ABSTRACT**

Impairments in the vascular effects of insulin, in part due to an imbalance in insulin stimulated endothelium-derived nitric oxide (NO) and endothelin-1 (ET-1) signaling, are associated with reductions in insulin-mediated glucose disposal with obesity, type 2 diabetes, and cardiovascular disease. We investigated the effects of metformin, daily physical activity, and aerobic fitness on the vascular reactivity to insulin in conduit and skeletal muscle resistance arteries of rats prone to insulin resistance, obesity, and type 2 diabetes. Our data indicate that metformin does not enhance the skeletal muscle microvascular reactivity to insulin, despite reductions in body weight, food consumption, and improvements in glycemic control in obese insulin resistant rats. In contrast, daily physical activity improved insulin-stimulated vasorelaxation of the aorta, an effect that was in part mediated by reduced insulin-stimulated ET-1 vasoconstriction. Additionally we report that low intrinsic aerobic fitness was paradoxically associated with greater insulin-mediated vasorelaxation and an exclusive dependence on NO in aortic vasomotor function. Collectively, our results provide strong evidence for physical activity-specific insulin-sensitizing effects on the vasculature with obesity.