Impairments in the vascular effects of insulin, in part due to an imbalance in insulin stimulated endothelium-derived nitric oxide and endothelin-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 (Chapter 2), or daily physical activity (Chapter 3) treatments, and aerobic fitness (Chapter 4) on the vascular reactivity to insulin in large conduit and skeletal muscle resistance arteries of rats prone to cardiometabolic disease. Our data indicate that metformin does not enhance 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, and reduced body weight and improved insulin sensitivity. These data indicate therapeutic benefits of physical activity over medications like metformin regarding the vascular actions of insulin. Additionally we report that low intrinsic aerobic fitness is associated with greater insulin-mediated vasorelaxation and an exclusive dependence on nitric oxide in vascular function of large conduit arteries. Collectively, these results provide strong evidence of physical activity's powerful insulin-sensitizing effects on the vasculature with obesity.