Obesity is leading cause of vascular disease in Western cultures but treatment of this disease is thwarted by a lack of mechanistic information regarding effects of obesity on the circulation. A key defect in vascular function in this population is the loss of endothelial vasodilation, thought to be secondary to increased oxidant stress. Exercise is well-documented to improve vascular function in obese subjects but links between fitness and improved outcomes are unknown. In this presentation, we offer new evidence that increased muscle mass induced by deletion of myostatin confers significant microvascular benefits in obese mice. These changes occur in parallel with improved metabolism and reduction in oxidant stress driven by activity of NADPH Oxidase 1 (NOX1). Further studies deleting NOX1 demonstrated reduced oxidant stress in obese mice despite continued metabolic deficiencies. Deletion of NOX1 normalized endothelial function, suggesting that NOX1 is the link between the improvement in vascular function observed when muscle mass is increased. These findings suggest that increased muscle may be a contributor to the improved vascular health seen when obese individuals exercise. This benefit occurs via reducing the oxidant stress caused by NOX1. Patients with larger muscle mass may explain the “fit but fat” population in which disease is less severe and conferring such benefits to afflicted populations may provide powerful therapy for vascular disease in obesity.