S28-1 The role of NOS-derived superoxide in vascular disorders

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Oxidative stress serves to damage the endothelium, leading to vascular dysfunction. Recently the role of dysfunctional nitric oxide synthase (NOS) is attracting attention as a superoxide-generating enzyme. Tetrahydrobiopterin (BH4) is the essential coenzyme for NOS to work as a NO producing enzyme, and when BH4 is deficient or lacking, NOS generates superoxide rather than NO (uncoupled NOS). Under pathological conditions with augmented oxidative stress, endothelial tissue level of BH4 is reduced by oxidization to BH2. The role of superoxide from uncoupled eNOS has been demonstrated as a mechanism of the reduced endothelium-dependent vasorelaxation in various vascular disorders. We demonstrated in eNOS-overexpressing transgenic mice that superoxide from eNOS lead to augmented atherosclerotic lesion formation under hypercholesterolemia. We also showed that vascular remodeling was augmented in diabetic mice. This augmentation was associated with increased superoxide generation from the endothelium and reversed by supplementation with exogenous BH4. Therefore superoxide from uncoupled eNOS is involved in not only impaired dynamic vascular function but also vascular structural disorders. In vascular disorders, the therapeutic strategy toward normalizing NOS function is important.