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MEETING ABSTRACT

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Regional heterogeneity of vascular dysfunction in *db/db* mice

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Background: It is well recognized that diabetes mellitus adversely affects the vasculature. However, whether various arteries exhibit differential vulnerability to the diabetic milieu remains to be explored. We compared the functional and molecular alterations in the aorta, carotid and femoral arteries in relation to the progression of the diabetic status in *db/db* mice and examined some plausible mechanisms underlying the differential adaptation of these arteries.

Methods: Using wiremyography, the vasodilatory and contractile responses of aortae, carotid and femoral arteries isolated from *db/db* and control mice at 6, 10 and 14 weeks of age were examined to assess the endothelial and vascular smooth muscles function. As well, protein expression of superoxide dismutase (SOD) isoforms were examined in the three arteries. In parallel, body weight, plasma glucose, C-reactive protein, 8-isoprostane, cholesterol and triglycerides were measured.

Results: There were age-related increases in body weight, plasma glucose, 8-isoprostane, C-reactive protein, and triglycerides in *db/db* mice. In comparison to the aorta and femoral artery, the carotid artery was the most resilient and maintained normal functional responses at the three age points examined. The aortae of *db/db* mice exhibited progressive loss of endothelium-dependent and -independent vasodilatation, while concurrently having enhanced vasoconstriction. The femoral arteries of *db/db* mice showed reduced endothelium-dependent, hyperpolarizing factor-mediated vasodilatation and attenuated contractile responses. The femoral arteries of control and *db/db* mice lacked the expression of SOD-3 in contrast to the aortae and carotid arteries.

Discussion: Substantial heterogeneity exists between the aorta, carotid and femoral arteries both at functional and molecular levels. The carotid artery maintained unaltered functional responses despite marked increases in systemic oxidative stress in *db/db* mice, likely because the carotid artery relaxed in response to superoxide anion or peroxynitrite; this response may reflect a physiological strategy to maintain blood supply to the brain under stressful conditions. Both the vasodilatory and contractile responses in the femoral arteries of *db/db* mice were attenuated, probably due to the lack of the expression of SOD-3 in the femoral arteries leading to marked oxidative damage. Understanding regional differences in vasomotor control, coupled with advanced drug delivery systems will help developing therapies that target specific vascular beds with reduced systemic side effects.

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