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Disturbed Blood Flow induces Arterial Stiffening Through Thrombospondin-1

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BACKGROUND:

Arterial stiffness and wall shear stress are powerful determinants of cardiovascular health, and arterial stiffness is associated with increased cardiovascular mortality. Low and oscillatory wall shear stress, termed disturbed flow *(d-flow)*, promotes atherosclerotic arterial remodeling, but the relationship between d-flow and arterial stiffness is not well understood. The objective of this study was to define the role of d-flow on arterial stiffening and discover the relevant signaling pathways by which d-flow stiffens arteries.

METHODS:

D-flow was induced in the carotid arteries of young and old mice of both sexes. Arterial stiffness was quantified ex vivo with cylindrical biaxial mechanical testing and in vivo from duplex ultrasound and compared with unmanipulated carotid arteries from 80-week-old mice. Gene expression and pathway analysis was performed on endothelial cell-enriched RNA and validated by immunohistochemistry. In vitro testing of signaling pathways was performed under oscillatory and laminar wall shear stress conditions. Human arteries from regions of d-flow and stable flow were tested ex vivo to validate critical results from the animal model.

RESULTS:

D-flow induced arterial stiffening through collagen deposition after partial carotid ligation, and the degree of stiffening was similar to that of unmanipulated carotid arteries from 80-week-old mice. Intimal gene pathway analyses identified transforming growth factor-β pathways as having a prominent role in this stiffened arterial response, but this was attributable to thrombospondin-1 (TSP-1) stimulation of profibrotic genes and not changes to transforming growth factor-β. In vitro and in vivo testing under d-flow conditions identified a possible role for TSP-1 activation of transforming growth factor-β in the upregulation of these genes. TSP-1 knockout animals had significantly less arterial stiffening in response to d-flow than wild-type carotid arteries. Human arteries exposed to d-flow had similar increases TSP-1 and collagen gene expression as seen in our model.

CONCLUSIONS:

TSP-1 has a critical role in shear-mediated arterial stiffening that is mediated in part through TSP-1's activation of the profibrotic signaling pathways of transforming growth factor-β. Molecular targets in this pathway may lead to novel therapies to limit arterial stiffening and the progression of disease in arteries exposed to d-flow.