P13: ARHGEF1/RHOA SIGNALING PARTICIPATE IN AGEING-INDUCED ARTERIAL STIFFNESS AND HYPERCOAGULABILITY

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The RhoA signaling pathway is a master regulator of mechanotransduction and plasticity of vascular smooth muscle cells (VSMCs) that controls arterial stiffening. The RhoA exchange factor Arhgef1 is causally involved in the development of angiotensin II-dependent hypertension.

Our aim was to determine whether Arhgef1 plays a key role in age-associated arterial stiffening and the coupling with modifications of the procoagulant properties of blood and VSMCs. We used 65 week-old transgenic mice invalidated for Arhgef1 (Arhgef1−/−) and age-matched controls (Arhgef1+/+). In vivo arterial diameter pressure, distensibility/arterial pressure and elastic modulus/circular stress curves at the level of carotid artery were recorded using an echotracking system (VEVO 770 Visualsonics Imaging) in anesthetized animals.

Systolic blood pressure, pulse pressure and heart rate were not different between mutant and control mice. Isobaric carotid distensibility was increased in Arhgef1−/− mice compared to Arhgef1+/+ mice. The elastic modulus/circular stress curves were shifted significantly rightwards in Arhgef1−/− mice compared to Arhgef1+/+ mice. Thrombin generation in blood and at the surface of VSMCs cultured from aorta was reduced in Arhgef1−/− mice. Anticoagulant markers secreted by the vascular wall (tissue factor pathway inhibitor and thrombomodulin) were increased in plasma of Arhgef1−/− mice.

The time of formation of an occlusive thrombus induced by FeCl3 in the carotid artery was prolonged in Arhgef1−/− mice.

In conclusion, the Arhgef1/RhoA contractile pathway contributes to arterial stiffening and VSMC procoagulant properties in aging. Whether this reduced procoagulant properties of the vascular wall is a cause or consequence of arterial stiffness remains to be elucidated.