**Role of C-type natriuretic peptide in the pathogenesis of aortic aneurysm**

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**Introduction & Aim:** Thoracicaortic aneurysm (AA) and abdominal AA are life-threatening diseases characterized by dilation, inflammation, and structural weakness; development of pharmacological therapies is desperately needed. CNP (C-type natriuretic peptide) plays a key role in vascular homeostasis, mediating vasodilator, anti-inflammatory, and antiatherogenic actions. As such processes drive AA, we determined the role of endogenous CNP in offsetting pathogenesis.

**Methods**: Tissue from patients with AA was analysed to determine the consequences on CNP signalling. Ascending and suprarenal aortic diameters were assessed at baseline and following Ang II (angiotensin II; 1.44 mg/kg per day) infusion in wild-type, endothelium-restricted (ecCNP−/−), fibroblast-restricted (fbCNP−/−), global CNP (gbCNP−/−), or global NPR-C−/− mice infected with an adeno-associated virus expressing a proprotein convertase subtilisin/kexin type 9 gain-of-function mutation or backcrossed to an apoE−/− background. At 28 days, aortas were harvested for RT-qPCR and histological analyses. CNP (0.2 mg/kg per day) was infused to rescue any adverse phenotype.

**Results:** Aneurysmal tissue from patients with thoracic AA and abdominal AA revealed that CNP and NPR-C (natriuretic peptide receptor-C) expression were overtly perturbed. ecCNP−/−, fbCNP−/−, and gbCNP−/− mice exhibited an aggravated phenotype compared with wild-type mice in both ascending and suprarenal aortas, exemplified by greater dilation, fibrosis, elastin degradation, and macrophage infiltration. CNP and NPR-C expression was also dysregulated in murine thoracic AA and abdominal AA, accompanied by increased accumulation of mRNA encoding markers of inflammation, extracellular matrix remodeling/calcification, fibrosis, and apoptosis. CNP also prevented activation of macrophages and vascular smooth muscle cells. An essentially identical phenotype was observed in NPR-C−/− mice and while administration of CNP protected against disease severity in wild-type animals, this phenotypic rescue was not apparent in NPR-C−/− mice.

**Discussion:** Endothelium- and fibroblast-derived CNP, via NPR-C activation, plays important roles in attenuating AA formation by preserving aortic structure and function. Therapeutic strategies aimed at mimicking CNP bioactivity hold potential to reduce the need for surgical intervention.