Unstable carotid atherosclerotic plaques cause stroke and lesions from those patients are abundant with activated mast cells at the sites of rupture. Recent data from our group showed a statistically significant upregulation of activated mast cells in low calcified whereas resting mast cells were upregulated in high calcified plaques, indicating that mast cells fractions may associate with various aspects of plaque pathology. Our hypothesis is that mast cell fractions associate with key features of plaque vulnerability such as calcification, intraplaque hemorrhage and other immune cell fractions.

Methods: The Biobank of Karolinska Endarterectomies prospectively enrolls patients (n = 1300) treated for carotid atherosclerosis in Stockholm, comprising BioBank with paraffin-embedded plaque tissues for histology, ImageBank with quantified diagnostic computed tomography images using VascuCap software and DataBank of 100 clinical variables as well as transcriptomics and proteomics large-scale datasets.

Results: Histologic stainings of plaque tissue microarrays confirmed the presence of mast cells in atheromatous lesions and revealed that mast cells were systematically found in Perls$^+$ regions. The average total number of mast cells per square millimeter per patient correlated negatively with the calcification content. In addition, immunohistochemical analysis demonstrated that mast cells correlate positively with CD3$^+$ cells while they did not correlate with markers of other immune cells. By stratifying the results according to patient symptoms, we found that activated mast cells were elevated in both symptomatic and asymptomatic patients and increased with severe symptoms of plaque instability. However, patients' medication does not impact mast cell regulation.

Conclusions: Systematic enumeration of mast cell fractions in human plaques indicates that activated mast cells associate with increased vulnerability, both when it comes to clinical patient symptoms and morphological plaque features.

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Inflammatory Activity of Human Perivascular Adipose Tissue in Abdominal Aortic Aneurysms

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Background: Perivascular adipose tissue (PVAT) contributes to vascular homeostasis and is increasingly linked to vascular pathology. PVAT density and volume were associated with abdominal aortic aneurysm (AAA) presence and dimensions in imaging techniques. However, mechanisms underlying the role of PVAT in AAA have not been clarified. Our study aimed to explore differences in PVAT from AAA using gene expression and functional tests.

Methods: Human aortic PVAT and control subcutaneous adipose tissue were collected during open AAA surgery. Gene analyses and functional tests were performed. The control group consisted of healthy aorta from nonliving renal transplant donors. Gene expression tests were performed to study genes potentially involved various inflammatory processes and AAA related genes. Live PVAT and subcutaneous adipose tissue from AAA were used for ex vivo co-culture with smooth muscle cells (SMC) retrieved from nonpathologic aortas.

Results: Adipose tissue was harvested from 27 AAA patients (n[gene expression] = 22, n[functional tests] = 5) and 5 control patients. An increased inflammatory gene expression of *PTPRC* ($P = .008$), *CXCL8* ($P = .033$), *LCK* ($P = .003$), and *CCL5* ($P = .004$) and an increase in extracellular matrix breakdown marker *MMP9* ($P = .016$) were found in AAA compared with controls. Also, there was a decreased anti-inflammatory gene expression of *PPARC* in AAA compared with controls ($P = .040$). SMC co-cultures from nonpathologic aortas with PVAT from AAA showed increased *MMP9* ($P = .033$) and *SMTN* ($P = .008$) expression and subcutaneous adipose tissue increased *SMTN* expression in these SMC.

Conclusions: Our data revealed that PVAT from AAA shows an increased proinflammatory and matrix metallopeptidase gene expression and decreased anti-inflammatory gene expression. Furthermore, increased expression of genes involved in aneurysm formation was found in healthy SMC co-culture with PVAT of AAA patients. Therefore, PVAT from AAA might contribute to inflammation of the adjacent aortic wall and thereby plays a possible role in AAA pathophysiology. These proposed pathways of inflammatory induction could reveal new therapeutic targets in AAA treatment.

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Polygenic Risk Score Identifies Patients at Increased Risk for Abdominal Aortic Aneurysm and May Benefit from Ultrasound Screening

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Background: Abdominal aortic aneurysm (AAA) is a significant heritable cause of cardiovascular related mortality, yet published genome-wide association studies have only identified 10 genome-wide significant ($P < 5 \times 10^{-8}$) risk loci to date. In addition, current AAA screening recommendations remain limited to men age 65 to 75 with a history of smoking. Genetic variants affecting multiple biological pathways are associated with AAA risk and may help to identify asymptomatic individuals at higher risk for disease.

Methods: Using electronic health record data, we identified individuals with and without clinical AAA in Million Veteran Program (MVP) participants. Individuals were genotyped on a customized Affymetrix array, and we tested 18 million genotyped and imputed DNA variants for association with AAA using logistic regression models adjusting for age, sex and population structure. We then performed replication in external datasets and set a $P < 5 \times 10^{-8}$ for statistical significance. In downstream analyses, we tested and validated a series of AAA polygenic risk scores (PRS) and assessed the associated AAA risk per standard deviation increase in PRS using prevalent data from an independent set of MVP participants (1656 AAA cases; 44,908 controls). We set a *P* value of less than .05 for statistical significance.

Results: We identified 7642 AAA cases and 172,172 controls. Following replication, we identified 14 novel AAA loci implicating known risk factors including lipids (*LPA, PCSK9*) and smoking (*CHRNA3*). We generated a 29 variant PRS and observed that a 1 standard deviation increase in the AAA PRS was associated with a 32% increased risk of AAA (odds ratio, 1.32; P_{PRS}

$= 1.7 \times 10^{-34}$). Men in MVP with the 5% highest PRS and over 50 years of age had a disease prevalence of 7.8% (142/1680), higher than that observed in AAA screening trials informing current guidelines.

Conclusions: Here, we identify novel AAA genetic associations with therapeutic implications and identify a subset of the population at significantly increased risk of AAA. Our data suggest that extending current screening guidelines to include testing for those with high polygenic AAA risk would significantly increase the yield of current screening.

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ABSTRACT SESSION III: AORTOPATHIES AND NOVEL VASCULAR DEVICES

The Perfuse Dual Chamber Stent Improves Donor Organ Recovery in a Porcine Model

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Background: Amid a critical shortage of organs for transplantation, ischemic injury from malperfusion during the agonal period remains a prohibitive barrier. We hypothesized that a dual chamber stent graft could isolate visceral perfusion from the agonal systemic circulation, while respecting the ethics of organ donation.

Methods: A retrievable dual chamber stent graft was welded from nitinol and covered with polymer. A central lumen maintained aortic flow, with an outer visceral chamber perfused by an oxygenator. Anesthetized pigs were assigned to either control (n = 7) or the dual chamber stent (n = 6). A 1-hour agonal phase of hypoxia (saturations <60%-70%) and hypotension (mean arterial pressure, <25 mm Hg) was simulated both medically and with partial balloon occlusion. The Perfuse stent visceral flow totaled 500 mL/min during the agonal phase followed by stent recapture and resuscitation to an end point of 2 days.

Results: Study groups had comparable agonal O_2 saturations, heart rate, and mean arterial pressure. Cardiac output and right ventricular end diastolic volume did not change during stent graft deployment. Compared with the low pO_2 of controls (48 mm Hg) and systemic stent animals (49 mm Hg), the visceral pO_2 averaged 413 mm Hg and visceral flow was significantly higher in stent animals. Five of seven controls were humanely killed from acute renal failure and volume overload; all stented animals survived without renal impairment. Transaminases were between 1.8- and 3-fold increase in control as compared with stented animals.

Conclusions: During a simulation of the agonal period, a dual chamber stent provided endovascular separation and marked improvement in perfusion and organ outcome. This goal was accomplished without significant impact on cardiac function, respecting current ethical considerations of the donation after cardiac death donor. The ability to separate the perfusion of the abdominal organs from the agonal systemic circulation without the need for open surgery might significantly improve the availability of donor organs for transplant.

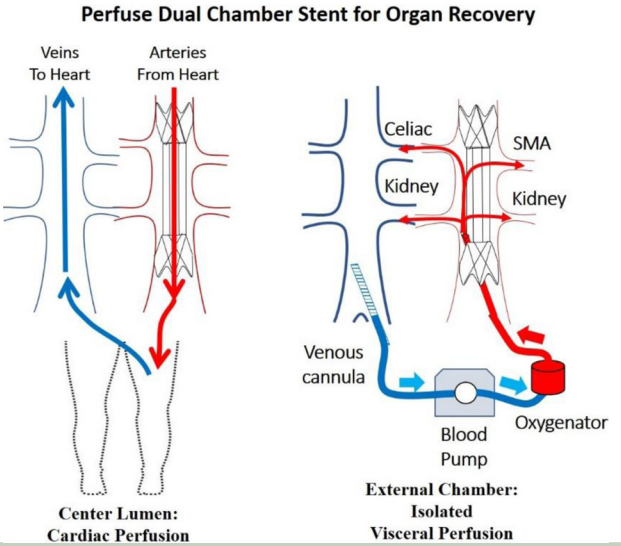

Fig.

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Maresin 1 Attenuates Murine Abdominal Aortic Aneurysms Via Vascular Smooth Muscle Cell-Dependent Transforming Growth Factor-β Signaling

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Introduction: The endogenous pro-resolving lipid mediator Maresin 1 (MaR1) is derived from the ω-3 polyunsaturated fatty acid docosahexaenoic acid and is involved in the resolution phase of inflammation. Specifically, MaR1 has been shown to attenuate inflammatory signaling in smooth muscle cells. It was hypothesized that exogenous administration of MaR1 would attenuate abdominal aortic aneurysm (AAA) growth via smooth muscle cell-dependent transforming growth factor (TGF)-β signaling.

Methods: AAAs were induced in C57BL/6 wild-type mice (n = 9 elastase + MaR1 [4 ng/g] or n = 10 elastase + vehicle) using an established topical elastase AAA model. Mice were treated with MaR1 or vehicle via intraperitoneal injection on days 7, 9, 11, and 13 after AAA induction. Abdominal aortas were harvested on day 14 for phenotypic evaluation of aortic diameter. Histologic analysis of smooth muscle actin (n = 3-4/group) and Western blot of TGF-β1 expression (n = 6-7/group) were performed. Additionally, AAAs were induced in smooth muscle cell specific TGF-β2 receptor knockout mice and treated with MaR1 (n = 7) versus vehicle (n = 10) and harvested on day 14 for phenotypic evaluation of aortic diameter. Groups were analyzed using one-way analysis of variance with the post hoc Tukey test and data presented as mean ± standard error of the mean.

Results: MaR1 treatment significantly attenuated AAA growth compared with vehicle (121.4 ± 9.4% vs 165.3 ± 9.4%; $P < .01$). A significant increase in aortic wall smooth muscle cell actin was identified in MaR1-treated mice compared with vehicle (27.1 ± 3.4% vs 14.2 ± 2.4%; $P = .03$). TGF-β1 expression was also significantly higher in MaR1 treated mice compared with vehicle ($2.95 \times 10^6 \pm 11.1 \times 10^5$ vs $1.63 \times 10^6 \pm 2.6 \times 10^5$ densitometry units; $P = .02$). Finally, smooth muscle cell-specific TGF-β2 receptor knockout mice showed no difference in AAA diameter in MaR1-treated mice compared with vehicle (133.9 ± 8.0% vs 123.8 ± 7.9%; $P = .4$).