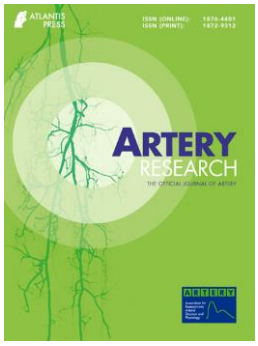

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5.1: ENHANCED COMMUNICATION VIA GAP JUNCTIONS PROTECTS THE ENDOTHELIUM FROM ISCHAEMIA-REPERFUSION INJURY IN VIVO IN MAN

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3.3
CARDIOTROPHIN-1 IS A DETERMINANT OF ARTERIAL STIFFNESS AND THICKNESS IN RODENTS

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Background & aims: Cardiotrophin-1 (CT-1), a cytokine belonging to the interleukin-6 family, exerts proliferative and secretory effects in vascular smooth muscle cells. We aimed to investigate the functional and morphological vascular changes induced by chronic CT-1 administration in rats and its involvement in the arterial phenotype of CT-1-null mice.
Methods: A) CT-1 (20 μg/Kg, IP) was administrated to Wistar rats for six weeks ($n = 10$/group). B) 2 year-old wild-type (WT) ($n = 12$) and CT-1-null mice ($n = 12$) were studied. Vascular structure and function were evaluated by an echo-tracking device. Circumferential wall stress, incremental elastic modulus (Einc), media cross-sectional area and pulse wave velocity (PWV) were measured. Aortic wall collagen, elastin and fibronectin contents were determined using immunohistochemistry, RT-PCR and Western blot.
Results: A) Neither vehicle nor CT-1 treatment modified BP. The Einc/wall stress curve from CT-1-treated was shifted to the left as compared with vehicle group. CT-1-treated rats also showed increased media cross sectional area ($p < 0.01$), collagen content ($p < 0.01$) and fibronectin expression ($p < 0.01$). B) CT-1-null mice presented an increased wall stress ($p < 0.05$) and Einc ($p < 0.05$) as compared with WT mice. Media cross sectional area, collagen and fibronectin content were reduced ($p < 0.05$) in mice lacking CT-1.
Conclusions: Normotensive rats subjected to CT-1 overloading developed impaired vascular function, characterized by an increment in arterial stiffness accompanied by an augmented media thickness and extracellular matrix production. Accordingly, CT-1-null mice presented a reduced arterial stiffness and a reduced media thickness and collagen content. Our data show that CT-1 is a key player in arterial thickness and stiffness.

3.4
INSTANTANEOUS BLOOD PRESSURE IS A DETERMINANT OF AORTIC AUGMENTATION INDEX AND PULSE WAVE VELOCITY: OBSERVATIONS IN PATIENTS WITH AUTONOMIC FAILURE

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Objective: Acute lowering of blood pressure (BP) with vasodilating agents is associated with a reduction in aortic augmentation index (AIx), whereas carotid-femoral pulse-wave velocity (cfPWV) is largely unaffected. We explored the effect of acute BP lowering on AIx and cfPWV in patients with autonomic failure (AF).
Design and method: Finger BP, Aix, cfPWV, heart rate (HR), left ventricular ejection time (LVET) and time to aortic wave reflection (TR) were obtained in supine rest and after 30^0 and 60^0 passive head-up tilting for 5 min in 10 subjects with autonomic failure (age 61 ± 15 yrs, 4 males).
Results: At baseline, MAP was 127 ± 22 mmHg, HR 72 ± 13 bpm, LEVT 338 ± 30 msec and TR 139 ± 4 msec. In response to 30^0 and 60^0 tilting MAP decreased by 18.7 ± 9.8 and $39.6 \pm 11.6\%$, LEVT by 11.5 ± 3.2 and $20.4 \pm 5.5\%$, AI_x by 39.2 ± 27.5 and $100.9 \pm 78.1\%$, cfPWV by 12.0 ± 10.5 and $27.5 \pm 13.5\%$ and HR increased by 5.2 ± 7.7 and $13.9 \pm 17.6\%$ (all $p < 0.05$), whereas TR did not change. Postural decreases in AI_x were not related to changes in cfPWV. In adjusted analysis, 68% of the AI_x variation during tilting could be explained by MAP and TR and 76% of the cfPWV variation by MAP and by gender.
Conclusion: Instantaneous BP is a determinant of AI_x and cfPWV in AF patients. Moreover, changes in AIx are unrelated to changes in cfPWV, indicating that these measures of vascular stiffness provide different information.

3.5
INVESTIGATING THE ROLE OF HEMODYNAMICS IN AAA FORMATION THROUGH COMBINED IMAGING AND MODELING: A LONGITUDINAL IN-VIVO STUDY IN APOE MICE

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The pathophysiological mechanisms underlying abdominal aortic aneurysm (AAA) formation are not yet fully understood. Hemodynamics have been suggested to play an important (modulating) role, but no longitudinal studies have been performed yet due to (a.o.) a lack of (human) data in the pre-diseased state. We used an established mouse model of AAA to perform a longitudinal hemodynamical study in 10 male apoE- deficient mice. All animals were scanned at baseline using micro-CT (Triumph, Gamma Medica) with a dedicated contrast agent (Aurovist, Nanoprobes) to assess the AA geometry, immediately followed by a baseline ultrasound scan (Vevo 2100, Visualsonics) to assess aortic structures and diameters and to measure Doppler velocity waveforms at the proximal and distal aorta and at the celiac, mesenteric, left and right renal arteries. All animals subsequently underwent implantation of a subcutaneous pump , continuously delivering angiotensin || for 28 days. End stage micro-CT and ultrasound scans were performed 31 days after pump implantation. Eight animals survived the complete experiment, and 5 of them developed an AAA. The micro-CT images were subsequently used to reconstruct a geometric 3D computer model (Mimics, Materialise) and combined with the measured flows in a Computational Fluid Dynamics (CFD) simulation (Fluent, Ansys). This procedure will provide unique data on the pre- and post-AAA hemodynamic situation (blood flow and wall shear stress patterns) over the abdominal aorta and side branches in great detail and will allow to further analyze the potential link between local hemodynamics, AAA formation and the location at which the aneurysm develops.

3.6
NANOMECHANICAL PROPERTIES OF A MODEL OF TYPE 1 DIABETIC AORTA

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Although it is well established that in both Type 1 and Type 2 diabetes arterial stiffening occurs, the differential roles played by constitutive arterial components remain unknown. Here, we characterised the nanomechanical properties of fibrillin microfibrils, a key elastic fibre component, extracted from diabetic arteries.
We isolated fibrillin microfibrils from the aortae of rats with a Streptozotocin-induced model of Type 1 diabetes, and age-matched controls. Fibrillin microfibrils have a 'beads-on-a-string' structure with a periodicity of approximately 56 nm. Atomic force microscopy (AFM) was used to image the microfibrils to determine whether there were any structural changes. Molecular combing was also used to apply a known tensile force (4000 pN) to partially adsorbed fibrillin microfibrils. Combed microfibrils were also imaged with AFM. Fibrillin microfibril periodicity was significantly reduced in the diabetic rats; 52.7 +/- 0.3 nm (diabetic) compared with control animals; 59.5 ± 0.4 nm ($n = 1500$ periodicity measurements, 3 animals per group; $p < 0.01$). Following combing, periodicity was significantly increased in microfibrils isolated from diabetic aortae (62.3 nm, SEM 0.51 nm, t-Test, $N = 1500$, $P < 0.01$) as compared with control animals (58.5 nm, SEM 0.40 nm, $p < 0.001$, t-test).
Eight weeks after islet cell destruction and hyperglycaemia, in vivo, profound changes in microfibril structure are induced, which in turn appear to weaken these important macro-molecular assemblies. This study also demonstrates that it is possible to localise structural and mechanical changes in diabetic aortae at the nanoscopic length scale.

5.1
ENHANCED COMMUNICATION VIA GAP JUNCTIONS PROTECTS THE ENDOTHELIUM FROM ISCHAEMIA-REPERFUSION INJURY IN VIVO IN MAN

S. Venkatasubramanian [1,*], C. M. Pedersen [1,2], J. P. Langrish [1], G. Barnes [1], C. M. Cheong [1], H. E. Botker [2], R. K. Kharbanda [3], N. L. Cruden [1], D. E. Newby [1], N. N. Lang [1]
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Background: : Endothelial dysfunction is the hallmark of ischaemia- reperfusion (IR) injury and intercellular gap junctions appear to play a role in this process. Rotigaptide (ZP-123) is a novel anti-arrhythmic agent that increases inter-cellular communication via gap junctions. We tested the hypothesis that rotigaptide protects the human forearm arterial circulation from IR induced endothelial dysfunction.
Methods: Healthy male subjects ($n = 21$) were recruited into a randomised double-blind cross-over study. IR injury (upper arm cuff inflated to 200 mmHg for 20 min) was induced in the presence of intra-arterial rotigaptide

(25 nmol/min) or saline placebo on separate visits. Using venous occlusion plethysmography, forearm arterial blood flow was measured during intra-arterial infusion of acetylcholine (ACh; 5—20 μg/min) or sodium nitroprusside (SNP; 2 - 8 mg/min) before and after IR injury.
Results: Resting blood flow remained unchanged throughout (P = NS). ACh and SNP caused arterial vasodilatation (P < 0.01) that was not affected by rotigaptide (P = NS). IR injury caused substantial impairment of ACh-induced vasodilatation (P = 0.007). This effect was abolished by rotigaptide. Endothelium-independent vasodilatation evoked by SNP was unaffected by either IR injury or rotigaptide (P = NS).
Conclusion: IR injury impairs endothelium-dependent vasomotion: an effect that is reversed by rotigaptide. This is the first clinical study to demonstrate that enhanced communication via gap junctions protects the endothelium from IR injury.

5.2
SOLUBLE EPOXIDE HYDROLASE INHIBITION PREVENTS CORONARY ENDOTHELIAL DYSFUNCTION IN MICE WITH RENOVASCULAR HYPERTENSION

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The study addresses the hypothesis that endothelial dysfunction in experimental arterial hypertension is related to an alteration in epoxyeicosatrienoic acids (EETs) pathway and can be prevented by the inhibition of EETs degradation by soluble epoxide hydrolase (sEH).
Arterial hypertension was induced in FVB mice using the two kidney-one clip (2K1C) model. Seven weeks after surgery, increased carotid artery pressures (Millar tonometer) and cardiac hypertrophy (echocardiography) were present in 2K1C mice as compared with control mice. Left coronary artery endothelium-dependent relaxations to acetylcholine was decreased in 2K1C mice without significant modification in the relaxing responses to NS309 and NS1619, the openers of calcium-activated potassium channels mediating the hyperpolarizing effect of EETs. The inhibitors of cytochrome epoxygenases, which synthesize EETs, fluconazole and MSPPOH impaired the coronary relaxations to acetylcholine in control mice but not in 2K1C mice. Moreover, sEH expression was increased in 2K1C mice. The sEH inhibitor AUDA administered five weeks after surgery in 2K1C mice for two weeks (drinking water: 25 mg/L) reduces arterial pressures and cardiac hypertrophy, improved the coronary relaxations to acetylcholine and restored the inhibitory effect of fluconazole and MSPPOH on acetylcholine-induced relaxations without modifying the relaxations to NS309 and NS1619.
These results demonstrate that a reduced EETs-mediated relaxations related to an increased degradation by sEH contributes to coronary endothelial dysfunction in hypertensive mice. The inhibition of sEH prevents the endothelial dysfunction by restoring EETs availability appearing thus as a promising pharmacological intervention to limit cardiovascular morbidity and mortality in arterial hypertension.

5.3
ISOLATED SYSTOLIC HYPERTENSION DOES NOT RESULT FROM A SMALLER PROXIMAL AORTIC DIAMETER

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It has been suggested that isolated systolic hypertension (ISH) may result from a smaller proximal aortic diameter. However, the available data are conflicting, no doubt because of different techniques and sites of measurement. We compared maximum (systolic) diameter, minimum (diastolic) diameter, and aortic distensibility at various levels along the thoracic aortic arch, between normotensive subjects (NT) and those with ISH, using MRI.
48 healthy subjects aged ≥ 60 years, free of cardiovascular disease and medication were recruited from the ACCT Study. A Fiesta sequence (1.5 T scanner,GE) was then performed in all subjects at 6 aortic levels: the aortic root (L1),1 cm above the aortic valve (L2), proximal to the innominate artery (L3), distal to the left subclavian artery (L4), the descending aorta (L5) and the level of the diaphragm (L6). Diameters were determined using ARTFUN software.
Subject were divided into those with a normal blood pressure (<140/90 mmHg) and those with ISH (systolic≥140 mmHg, diastolic <90 mmHg), and were matched for age. Average systolic and diastolic aortic diameters were greater in subjects with ISH (Table 1). Distensibility was greater in normotensive subjects compared to those with ISH at L2-L6 (L1: 0.64 ± 2.72 vs. 0.21 ± 1.53; L2: 5.69 ± 2.72 vs. 2.60 ± 1.33; L3: 3.10 ± 1.97 vs. 1.27 ± 0.99; L4: 3.86 ± 1.81 vs. 1.69 ± 0.70; L5: 3.91 ± 2.58 vs. 1.68 ± 0.63; L6: 5.18 ± 2.43 vs. 2.73 ± 1.69, units = 10^{-3} x $mmHg^{-1}$, P < 0.01 for L2-L6, P = 0.5 for L1). With the exception of the aortic root, both systolic and diastolic proximal aortic diameters are greater in subjects with ISH compared to NT subjects, whereas distensibility is reduced.

Table 1.

Aortic Level	Systolic Diameter (cm) NT	Systolic Diameter (cm) ISH	P	Diastolic Diameter (cm) NT	Diastolic Diameter (cm)ISH	P
L1	3.09 ± 0.41	3.18 ± 0.28	0.317	3.05 ± 0.41	3.18 ± 0.24	0.331
L2	3.15 ± 0.44	3.41 ± 0.37	0.019*	3.03 ± 0.45	3.33 ± 0.36	0.012*
L3	3.06 ± 0.34	3.27 ± 0.33	0.038*	2.91 ± 0.37	3.19 ± 0.34	0.030*
L4	2.55 ± 0.21	2.85 ± 0.32	0.003*	2.39 ± 0.22	2.74 ± 0.31	<0*
L5	2.43 ± 0.24	2.66 ± 0.28	0.011*	2.30 ± 0.24	2.56 ± 0.27	0.004*
L6	2.34 ± 0.24	2.44 ± 0.25	0.112	2.15 ± 0.23	2.30 ± 0.22	0.044*

5.4
HERITABILITY OF RETINAL PHENOTYPES IN A EUROPEAN POPULATION

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Background: The retinal arterioles and venules are accessible for non-invasive visualisation, hereby providing a means to study the early structural changes and pathological features of the microcirculation. To our knowledge, the heritability of these phenotypes has not yet been assessed in a general European population.
Methods: Nuclear families were randomly recruited from a Flemish (Caucasian) population. Phenotyping was performed using a non-mydriatic digital camera (Canon Cr-DGi, Canon, Tokyo, Japan), and images were post-processed using validated software (IVAN, as used in the ARIC study) to generate central retinal arteriole (CRAE) and venule (CRVE) equivalents. The arteriole-to-venule ratio (AVR) was calculated according to the Parr-Hubbard formula. Heritability was assessed with the ASSOC-program (S.A.G.E. [2009] Statistical Analysis for Genetic Epidemiology, Release 6.0.1: http://darwin.cwru.edu/). Sex and age were considered as covariables.
Results: Mean age of the participants was 46.7 ± 7.6 years, with 50.3% women. The current analysis included 167 pedigree members and 24 singletons. In unadjusted models, heritability was 0.33 for CRAE, 0.18 for CRVE and 0.35 for AVR (p for all <0.0001). In models accounting for sex and age, heritability was 0 for CRAE, 0.39 for CRVE (p < 0.0001) and 0.25 for AVR (p < 0.0001)
Discussion: The heritability of retinal phenotypes was moderate. These findings suggest that genetic factors play a relevant role in the structure of the microcirculation. Further research is needed to identify which genes are associated with these phenotypes.