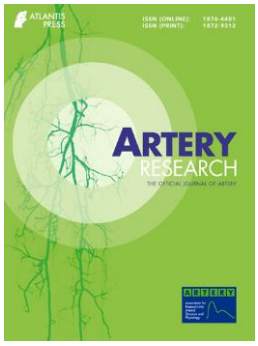

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5.4: HERITABILITY OF RETINAL PHENOTYPES IN A EUROPEAN POPULATION

T. Richart, M. Bochud, L. Thijs, Y. Jin, T. Kuznetsova, H.A.J. Struijker-Boudier, J.A. Staessen

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(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.