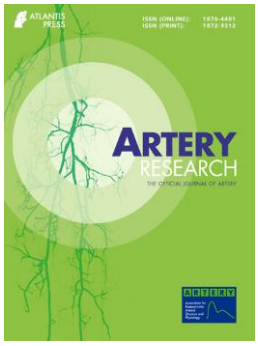

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07.06: LONG TERM ORAL CONTRACEPTIVE USE IS AN INDEPENDENT RISK FACTOR FOR ARTERIAL STIFFENING

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07.04
LOEYS-DIETZ SYNDROME (LDS): IN VITRO STUDIES OF SKIN FIBROBLASTS SHOWING DIFFERENCES BETWEEN MUTATIONS IN THE TGFBR1 AND TGFBR2 GENES

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LDS is a newly described condition caused by mutations in the genes encoding transforming growth factor-beta (TGF-B) receptors 1 and 2. The condition is associated with vascular tortuousity and formation and rupture of arterial aneurysms. Skin fibroblasts were cultured from 3 patients with confirmed LDS. All 3 cases had typical phenotypic features including a dilated aortic root and tortuous aortic arch and branches. DNA analysis revealed in case 1 a missense mutation of *TGFBR1* gene (c.722C>T), in case 2 a missense mutation of *TGFBR1* (c.1460G>A) and in case 3 a missense mutation of *TGFBR2* (c.1583G>A). *In vitro* studies of skin fibroblasts from these patients indicated that both patients carrying mutations of *TGFBR1* demonstrated a significant deficiency in the net expression of elastin and fibrillin genes (assessed by RT-PCR) and did not deposit elastic fibers in primary cultures. In contrast, they produced normal levels of auxiliary components of elastic fibers (fibulins 1, 2 and 5) and deposited normal collagen fibers. Interestingly, fibroblasts derived from patients with mutation of *TGFBR2* genes produced normal components of elastic fibers, but displayed intracellular retention of collagen type 1 and had significantly lower deposition of mature collagen fibers. Our findings indicate that the clinical manifestations associated with *TGFBR1* and 2 mutations, although similar, are caused by different mechanisms.

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07.05
PERIPHERAL AND CENTRAL PRESSURE WAVEFORM PARAMETERS ARE ASSOCIATED WITH NORMAL TENSION AND PRIMARY OPEN-ANGLE GLAUCOMA

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Aims: To investigate the association of peripheral and central pulsatile blood pressure with normal tension glaucoma (NTG) and primary open-angle glaucoma (POAG).
Methods: Radial pressure pulse waveforms were recorded in 110 glaucoma patients and central blood pressure calculated using a validated transfer function. Glaucoma was defined as definite neuroretinal rim loss assessed by stereo disc assessment, with corresponding confirmed field defect. Diagnosed and current intraocular pressure were recorded as was disease progression within the last 3 years. Comparison was drawn between NTG and POAG, and age/sex matched controls.
Results: Self-reported white coat hypertensives were excluded, leaving 70 POAG and 33 NTG patients, age 67±12 yrs, BMI 22±5 $kg.m^{-2}$, 55 male. Peripheral and central pulse pressures were lower in glaucoma patients than controls ($p<0.01$ and $p<0.0001$ respectively). Ocular diastolic and pulse perfusion pressures were lower in subjects with glaucoma ($p<0.01$). POAG patients had a lower peripheral form factor ((mean-diastolic)/pulse pressure) than NTG patients (0.34 and 0.36, $p<0.01$). The subendocardial viability ratio (SEVR) was lower in NTG than in POAG (1.71 and 1.56, $p<0.05$) and was negatively associated with glaucoma progression (1.58 in progression, 1.72 stable glaucoma, $p<0.05$) suggesting a role of diastolic blood perfusion in the eye, an organ that itself has a positive internal pressure.
Conclusions: These results indicate that pressure pulsatility and ocular perfusion, especially during diastole, are contributing factors in glaucoma and the progression of the disease.

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07.06
LONG TERM ORAL CONTRACEPTIVE USE IS AN INDEPENDENT RISK FACTOR FOR ARTERIAL STIFFENING

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Background: Oral contraceptives (OC) are among the most frequently used drugs in the world. We describe the population effects of current and long-term OC exposure on carotid-femoral pulse wave velocity (PWV).
Methods: The Asklepios study is a representative sample (n=2524, aged 35-55 years, 1301 women) from the Belgian general population, free from overt cardiovascular disease. The subjects were extensively screened; carotid-femoral PWV was measured using Doppler echography.
Results: Of 1301 women (median age 45.7 years), 27.4% were actively taking OC. However, past use of OC is far more prevalent with 81% having taken OC (median exposure 13 years).
Age-adjusted PWV was higher in women currently taking OC: 6.75 versus 6.55 m/s (difference 0.19±0.09 m/s; p=0.034). However, current OC users also had higher blood pressures (BP): systolic +4.4±0.9 mmHg, $p<0.001$; diastolic +2.3±0.6 mmHg, $p<0.001$. After adjustment for BP, the difference in PWV between current OC users and non-users became non-significant: 6.60 versus 6.62 m/s (difference 0.02±0.09 m/s; p=0.814). Duration of OC use, in contrast, remained a significant determinant of PWV, even after adjustment for age, BP, lipids, body size, heart rate, drug therapy (lipid-lowering, antihypertensive), glycemic status and smoking: F=6.1; p=0.013. Per 10 years of OC exposure PWV increased by 0.10 m/s (0.02—0.18; p=0.013).
Interpretation: Use of OC is associated with increased vascular stiffness. Current use is associated with increased PWV because OC's increase BP, long-term use (probably through structural remodelling of the vessels) is an independent determinant of PWV, increasing PWV by 0.1 m/s per 10 years of exposure.

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POSTER PRESENTATIONS

P1.01
TREATMENT WITH DEXAMETHASONE REVERSES IMPARED ELASTOGENESIS AND COLLAGENOGENESIS IN CULTURES OF FIBROBLASTS FROM PATIENTS WITH LOEYS-DIETZ SYNDROME (LDS)

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LDS is an autosomal dominant condition caused by mutations in the *TGFBR1* and *TGFBR2* genes. The condition is associated with vascular tortuousity and formation and rupture of arterial aneurysms. Recent successful use of losartan in the Marfan mouse model has raised hope for medical treatment of LDS. Here we report a promising *in vitro* response in dexamethasone-treated cultured fibroblasts from three LDS patients. All 3 cases had typical phenotypic features including a dilated aortic root and tortuous aortic arch and branches. DNA analysis revealed in case 1 a missense mutation of *TGFBR1* gene (c.722C>T), in case 2 a missense mutation of *TGFBR1* (c.1460G>A) and in case 3 a missense mutation of *TGFBR2* (c.1583G>A). *In vitro* studies of skin fibroblasts from these patients indicated that both patients with *TGFBR1* mutations demonstrated a significant deficiency in the expression of elastin and fibrillin genes (RT-PCR). In contrast, they deposited normal collagen fibres. Fibroblasts derived from the patient with a *TGFBR2* mutation produced normal elastic fibers, but displayed intracellular retention of collagen type 1 and significantly lower deposition of mature collagen fibers. Addition of 10-5M of dexamethasone to cultured fibroblasts restored normal elastogenesis in cultures of fibroblasts with mutations of *TGFBR1* gene and normalized collagen fiber production in fibroblasts carrying *TGFBR2* gene mutation. Further studies are needed to establish whether dexamethasone can have a therapeutic effect in patients with LDS. Prenatal treatment of affected fetuses may prevent or ameliorate the clinical manifestations of this disorder.

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P1.02
COMPARISON OF THE EFFECTS ON CENTRAL BLOOD PRESSURE OF A COMBINATION OF ATORVASTATIN WITH AMLODIPINE-BASED OR ATENOLOL-BASED ANTIHYPERTENSIVE THERAPY: AN ASCOT-LLA SUBSTUDY

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Background: HMG CoA reductase inhibitors (statins) lower serum cholesterol and reduce cardiovascular events in hypertensive subjects. It has been suggested that statins may also reduce brachial blood pressure (BP) modestly, but their effect on central (aortic) BP is unknown. We investigated the effect of atorvastatin on central BP in a substudy of the lipid lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA).
Methods: 142 (age = 43 - 79 years; 127 male) hypertensive patients with total cholesterol ≤6.5mmol/L were randomized to atorvastatin 10mg or placebo in combination with amlodipine-based or atenolol-based antihypertensive treatment in a 2 x 2 factorial design. Central BP was measured by carotid artery tonometry. Data are means ± SE.