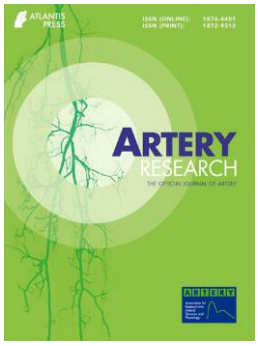

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07.04
LOEYS-DIETZ SYNDROME (LDS): IN VITRO STUDIES OF SKIN FIBROBLASTS SHOWING DIFFERENCES BETWEEN MUTATIONS IN THE TGFBR1 AND TGFBR2 GENES

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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.

Results: Brachial BP was similar between atorvastatin and placebo groups. Carotid systolic BP was slightly lower in the atorvastatin group but there was a statistically significant interaction between lipid-lowering and antihypertensive regimen; carotid SBP was lower in people randomized to atorvastatin + amlodipine-based therapy (placebo + atenolol = 130.6±2.4mmHg; atorvastatin + atenolol = 132.1±2.3mmHg; placebo + amlodipine = 131.0±2.8 mmHg; atorvastatin + amlodipine = 122.5±2.3 mmHg; Interaction p = 0.04; comparison placebo + amlodipine vs. atorvastatin + amlodipine p < 0.01).
Conclusions: The combination of atorvastatin with amlodipine-based antihypertensive treatment lowers central BP. This effect may contribute to the reduced incidence of cardiovascular events seen in people receiving this combination in ASCOT-LLA.

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P1.03
DIFFERENCES IN THE LATE SYSTOLIC SHOULDER PRESSURE (SBP2) OF THE RADIAL ARTERY PRESSURE WAVEFORM BY ANTIHYPERENSIVE REGIMEN IN THE ANGLO SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT)

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Previous work using a transfer function to estimate central systolic blood pressure (SBP) from the pressure waveform in the radial artery reported that, central SBP was lower in the amlodipine-based regimen compared with the atenolol-based regimen in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [1]. However use of a transfer function to estimate central BP has been criticised and more recently Munir et al.,[2] have proposed that the late systolic shoulder ($pSBP_2$) may be a direct estimate of central SBP. We compared $pSBP_2$ between patients randomized to the amlodipine-based and atenolol-based regimens in a substudy of ASCOT.
229 patients participated in the substudy. Applanation tonometry was performed at the right radial artery using a Millar tonometer. Waveforms were ensemble averaged and calibrated to brachial artery pressure. All data are means (SD).
Brachial BP did not differ significantly (137.5 (12.2)/79.6 (7.4) vs. 142.1 (15.3)/80.5 (9.2) mmHg; NS), but $pSBP_2$ was significantly lower in the amlodipine-based regimen (112.4 (10.4) vs. 119.3 (13.1) ; p< 0.01). $pSBP_2$ occurred earlier in the amlodipine-based group (415.8 (53.0)vs. 453.5 (51.6) ms; p < 0.01) probably due to the lower heart rate in the atenolol-based regimen.
Lower $pSBP_2$ in people randomized to the amlodipine-based regimen in ASCOT are in keeping with previous findings using a transfer function applied to the radial pressure waveform and direct measurements in the carotid artery and suggest that $pSBP_2$ may be a useful indicator of central SBP.
1. Williams et al., Circulation 2006; 113:1213-25
2. Munir et al., Hypertension. 2008;51:112-8.

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P1.04
THE INFLUENCE OF QUINAPRIL ON ARTERIAL STIFFNESS, BLOOD VISCOSITY AND ARTERIAL SHEAR STRESS IN PATIENTS WITH ESSENTIAL ARTERIAL HYPERTENSION

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Aim: to analyze the influence of quinapril on aortic PWV, whole blood viscosity (WBV), shear stress in the ascending aorta (AA) and common carotid artery (CCA), prometaloproteinase-1 (proMMP-1) and its tissue inhibitor (TIMP-1) plasma concentration in patients with essential arterial hypertension (HT).
Methods: 55 patients, (mean age 55,8 ± 13,8 yrs.) with HT 1 and 2 gr. were treated with quinapril in stepwise increased doses from 10 to 40 mg/d till BP goal <140/90 mmHg was achieved. At baseline and then after 3 and 6 months of treatment PWV, WBV, proMMP-1 and TIMP-1 were determined. Shear stress in AA and CCA was calculated from WBV, internal vessel diameter and blood flow velocity (Vmax) measured ultrasonographycally.
Results: After 6 months of treatment by quinapril we observed decrease of BP (155.6/92.0 mmHg vs. 135.9/82.9 mmHg, p<0.001), PWV (10.35 m/s vs. 9.64 ms, p<0.001), WBV (5.14 cP vs. 4.86 cP, p<0.05) and TIMP-1 (111.0 ng/ml vs. 94.1 ng/ml, p<0.001) and increase of Vmax in AA (127.1 cm/s vs.131.3 cm/s, p<0.05, Vmax in CCA (69.9cm/s vs. 78.4 cm/s, p<0.05) and shear stress in CCA (22.2 dyne/cm^2 vs. 24.7 dyne/cm^2 , p<0.05). Significant positive correlation was observed for PWV and TIMP-1, and negative correlations for PWV and Vmax in AA, PWV and Vmax in CCA, as well as PWV and shear stress in CCA.
Conclusions: Quinapril reduces arterial stiffness by inhibition of collagen metabolism. This effect is mediated by influence on arterial shear stress.

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P1.05
INFLUENCE OF FELODIPIN ON BLOOD PRESSURE AND ARTERIAL PROPERTIES IN OLDER HYPERTENSIVE PATIENTS

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Pulse wave velocity (PWV) and endothelial function are prognostic factors in arterial hypertension. Modification of them, apart from blood pressure (BP) lowering seems to be important in the evaluation of antihypertensive drugs. The AIM of this study was to prove otherwise while assessing the direct effect of felodipin (Felodip, Teva) on arterial properties in patients (more then 55 years old) with mild, moderate and severe hypertension.
Materials and methods: 30 hypertensive patients (mean age 63,98±6,46 years, 22 male, 8 female) received felodipin in individual titrated doses 2,5-10mg (mean dose 7,96 mg) daily for 3 months. The examination comprised routine tests, ECG, blood glucose, total cholesterol, triglycerides. The assessment of arterial stiffness was done by way of measuring brachial-ankle pulse wave velocity (baPWV). Endothelial function was calculated based on flow-mediated dilatation (FMD) parameters.
Results: The treatment produced a significant reduction in systolic (-30.4mmHg) and diastolic BP (-15.2mmHg). Significant decrease of baPWV (by 7.0%) and increase of FMD (by 21.5%) was observed. There was an insignificant rise in the levels of cholesterol, triglycerides, glucose. Felodipin has been well tolerated in most patients.
Conclusion: These results demonstrate that felodipin increases arterial distensibility. This effect of felodipin should be attributed to BP lowering and endothelial function improvement.

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P1.06
THE EFFECT OF SPINAL ANESTHESIA ON BLOOD PRESSURE AND AUGMENTATION INDEX

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Objectives: Parameters characterizing arterial stiffness - augmentation index (AIx) and pulse wave velocity (PWV) - are autonomous and independent cardiovascular risk factors. In this study we examined if the spinal anesthesia has considerable effects on the peripheral and central blood pressure, augmentation pressure, AIx and PWV.
Methods: The measurements were carried out using SphygmoCor (AtCor Medical, Australia) device. Spinal anesthesia was performed in all patients because of surgery, due to varicosity of lower extremity. Spinal anesthesia was performed uniformly by 3.2 milliliters of bupivacaine (0.5 %) via the L3 interstice. One liter of crystalloid infusion was administrated before the procedure. Patients were examined before anesthesia, and after enrollment of sensory analgesia and motor block.
Results: 29 patients (10 males and 19 females, aged: 53.7±12.9 years) were included in the study. As a result of spinal anesthesia not only the systolic (143.4±20.4 vs. 119.5±16.4 mmHg, p<0,0001) and diastolic peripheral (83.2±11.3 vs. 68.3±10.7 mmHg, p <0.0001), but also the systolic 132.6±18.3 vs. 105.2±14.8 mmHg, p<0.0001) diastolic (85.8±12.1 vs. 69.3±11.2, p<0.0001) central BP, mean pressure (105.8±13.9 vs. 84.7±13.1, p< 0.0001) and pulse pressure (60.2±13.9 vs. 51.2±10.8, p<0.02) decreased. We also observed a significant difference in the augmentation pressure (14.6±7.9 vs. 6.1±3.8 mmHg, p<0.001), and AIxHR75 (26.8±6.9 vs. 15.1±10.9%, p<0.001), respectively. There were no significant difference in PWV (9.3±3.7 vs. 9.1±3.4 m/s, p=0.8).
Conclusion: As a result of spinal anesthesia and so regional sympathetic nervous block not only the peripheral and central BP, but also the AIx decreased significantly, while PWV remained unchanged.

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