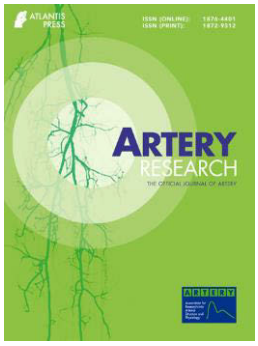

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07.04: LOEYS-DIETZ SYNDROME (LDS): IN VITRO STUDIES OF SKIN FIBROBLASTS SHOWING DIFFERENCES BETWEEN MUTATIONS IN THE TGFBR1 AND TGFBR2 GENES

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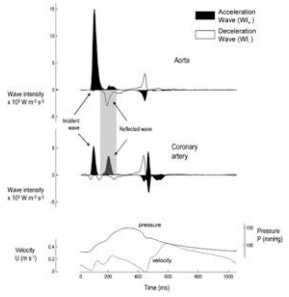
due to an increase in aortic stiffening (pulse wave velocity, r= 0.77, p<0.001).
Conclusions: Reflected wave can be followed travelling-back from the proximal aorta into the coronary arteries. These reflected waves augment coronary systolic blood flow. With increasing age the degree of augmentation of systolic coronary blood flow is increased.



doi:10.1016/j.artres.2008.08.302

07.01
OUTWARD HYPERTROPHIC REMODELING AND INCREASED CAROTID ARTERY WALL STIFFNESS IN PATIENTS WITH RUPTURED INTRACRANIAL ANEURYSMS

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Because an underlying arteriopathy might contribute to the development and rupture of intracranial aneurysms (IAs), we assessed the elastic properties of proximal conduit arteries in 27 patients with antecedent of ruptured IAs (delay: 4.8±0.6 years) and 27 control subjects. Arterial pressure, diameter, intima-media thickness (IMT), circumferential wall stress (CWS) and elastic modulus were determined in the common carotid arteries using applanation tonometry and echotracking. Moreover, carotid augmentation index (AIx) and carotid-to-femoral pulse wave velocity (PWV) were assessed.
Compared to controls, patients with IA exhibit higher carotid systolic (108±2 vs. 122±3 mmHg), diastolic (73±1 vs. 81±1 mmHg) and pulse pressures (35±1 vs. 41±2 mmHg), an increased IMT (0.55±0.01 vs. 0.64±0.01 mm, all P<0.01) without difference in diameter. IMT was correlated with pulse pressure in controls (r=0.539, P<0.001) but not in patients (r=0.152, P=0.2). Despite a similar CWS between groups, patients display an increased elastic modulus (0.21±0.02 vs. 0.37±0.03 kPa.10^3, P<0.001). These increased IMT and modulus were still observed in patients matched with controls for carotid arterial pressures (n=17 in each group). Furthermore, patients with IAs have higher PWV (7.8±0.2 vs. 8.3±0.2 m.s^{-1}, P<0.05) which contributes to the increase in arterial wave reflections (AIx: 15.8±2.1 vs. 21.1±1.6%, P<0.05) and thus in systolic and pulse pressures.
This study demonstrates that patients with IAs display a particular carotid artery phenotype with a partly pressure-independent outward hypertrophic remodeling and altered elastic properties which might contribute together with the fatiguing effect of increased pulsatile stress on the arterial wall, to the pathogenesis of IAs.

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07.02
TOWARDS NON-INVASIVE ASSESSMENT OF RENAL ARTERY STENOSIS SEVERITY IN THE INDIVIDUAL PATIENT WITH THE AID OF NUMERICAL COMPUTER SIMULATIONS

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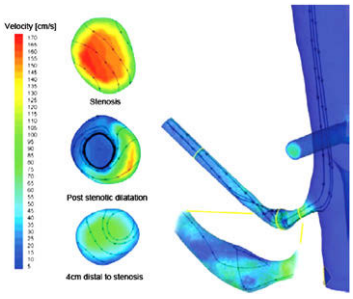
Introduction: Severe renal artery stenosis is responsible for 5% of all hypertension cases. Treatment of the stenosis is often decided upon catheterisation, with a pressure gradient (DP) of 10mmHg used as cut-off, thus requiring invasive measurements. The aim of the present study was to assess the feasibility and accuracy of a non-invasive estimate of DP through numerical simulation in a patient-specific model.
Methods: We constructed a computer model of the abdominal aorta, coeliac trunk, mesenteric superior aorta and two renal arteries from a patient with unilateral renal stenosis (77% area stenosis). Images were obtained from MR angiography scans and segmented to obtain the 3D patient-specific model. Blood flow was simulated assuming an aortic inflow rate of 2.7l/min and prescribed outflow rates at the different arterial outlets. The calculated DP was compared to in vivo measurements.



Results: The numerical calculations yielded a DP of 11.7mmHg, which was in excellent agreement with the value of 10.5mmHg measured in vivo in the same patient (with pressure guide-wires) and with values measured in a silicon hydraulic bench model of the same geometry. A parameter study demonstrated a rapid increase in DP beyond 60% stenosis. In the post-stenotic dilatation zone, secondary flow patterns with recirculation were observed.
Conclusion: These promising results demonstrate the feasibility and utility of patient-specific computer simulations in the diagnosis of individual patients, although further steps will be necessary to include pulsatile blood flow, distensible walls and patient-specific boundary conditions.

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07.03
FETUIN-A IS INDEPENDENTLY ASSOCIATED WITH PROGRESSIVE AORTIC STIFFNESS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Background: There is a disproportionate burden of vascular disease in patients with chronic kidney disease (CKD). Both aortic stiffness, as measured by carotid-femoral pulse wave velocity (C-F PWV), and deficiency in inhibitors of vascular calcification, such as Fetuin-A, have been implicated in the higher rates of cardiovascular mortality observed in this population. We sought to determine whether Fetuin-A concentration was inversely associated with progressive aortic stiffness.
Methods: 54 stable outpatients enrolled in a prospective cohort study of cardiovascular risk in CKD stages 3 and 4 underwent measurement of C-F PWV using Complior under standardized conditions at baseline and 12 months. Baseline plasma Fetuin-A concentration was determined using the Biovendor ELISA kit.
Results: The population was aged 68.0±10.4 years, 80% male, 11% diabetic with a mean eGFR of 32.0±11.5. Baseline Fetuin-A did not correlate with patient age, eGFR, mean arterial blood pressure, albumin, calcium-phosphate product, parathyroid hormone or CRP. Baseline Fetuin-A was inversely correlated with the change in PWV over 1 year (rho=-0.52, p<0.001). After adjustment for change in mean arterial pressure between visits, age, eGFR and presence of diabetes the correlation was maintained (r_p=-0.54, p<0.001). Using stepwise multiple linear regression with a model including age, change in eGFR, parathyroid hormone, CRP and diabetic status, Fetuin-A was the only independent predictor of change in aortic stiffness adjusted for change in MAP (β-coefficient -0.61, p<0.001; R^2 total 0.36).
Conclusion: In a cohort of patients with CKD stages 3 and 4 there is an independent negative association between Fetuin-A and progressive aortic stiffness.

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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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Imperial College London, London, United Kingdom

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.