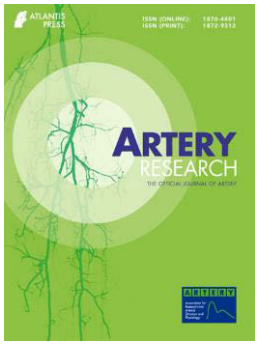

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P2.02: IMPACT OF RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS ON ARTERIAL WALL STIFFNESS

A. Cypiene, A. Venalis, J. Dadoniene, R. Rugiene, L. Ryliskyte, Z. Petrulioniene, M. Kovaite, V. Skorniakov, A. Laucevicius

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role of arginase pathway in response to shear stress has never been investigated.
Methods: To evaluate the regulation of arginases by different shear stress patterns without neuroendocrine factors, we perfused carotid arterial segments for 3 days to unidirectional high and to low oscillatory shear stress hemodynamic conditions. We compared these well-controlled measurements to an *in vivo* model of shear stress-induced atherogenesis. Vasoreactivity, immunohistochemistry and Western blot were used to characterize the role of arginase pathway.
Results: Our results from *ex vivo* perfusion arteries showed for the first time that exposure of carotid to oscillatory flow significantly increase arginase II protein expression and activity as compared to high shear stress flow condition (athero-protective). Our data suggested that arginase I and II are also regulated by shear stress *in vivo*. Arginases were up-regulated on EC, SMC and macrophages of carotid segments exposed either to low stress or to oscillatory shear stress conditions. Both plaque size and composition were differentially modulated in mice chronically treated with arginase inhibitor, nor-ω- hydroxy-nor-L-arginine for 9 weeks (10mg/kg/day, i.p)
Conclusions: The present study demonstrates that arginase expression is already modulated by 3 days exposure to different shear stress patterns in carotid arteries perfused *ex vivo*. Similar findings are also observed in a model of shear stress-induced atherogenesis *in vivo*.

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P1.58
ABNORMAL VASCULAR FETAL PROGRAMMING IN RATS SUBJECTED TO MATERNAL DIABETES

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Epidemiologic studies have clearly identified modifications of fetal environment as a risk factor for the development of cardiovascular diseases in adulthood.
In our experimental model, rats exposed *in utero* to maternal diabetes develop an hypertension as early as 6-month of age. In order to determine if the development of this hypertension results from an abnormal vascular fetal programming, gene expression profile of the aorta was studied on oligonucleotides chips (Agilent, G4130, 22k). Arterial structure and elastic properties were assessed on 3-(non-hypertensive stage) to 18-month-old rats from control (CMO3 and CMO18) and diabetic mothers (DMO3 and DMO18), with echo-tracking device and histomorphometry. DMO had a significantly higher SBP than CMO at 6 and 18 months of age (DMO18 : 218±3 mmHg vs CMO18 : 155±2 mmHg). DMO3 are characterized by an over-expression of subunits of P450 (Cyp4f4, Cyp4f2, Cyp8b1) and an under-expression of prostacyclin receptor, which both could contribute to vasoconstriction. Carotid elastic properties were not significantly different between CMO and DMO at 3 and 6 months. Surprisingly, thoracic aorta of DMO was not significantly thicker than CMO at 6 and 18M, in spite of the higher level of SBP in DMO. The lack of BP-induced wall thickening in DMO3 can be related to the under-expression of genes coding for proteins involved in migration and cell-matrix interaction (Evl, Ckap4, Dcamkl1). In conclusion, these results suggest an abnormal vascular fetal programming in rats exposed *in utero* to maternal hyperglycemia, which could explain the structural and functional arterial disorders observed in this model.

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P1.59
CHARACTERISTIC IMPEDANCE IN ISOLATED MOUSE LUNGS IS INVERSELY PROPORTIONAL TO PROXIMAL ARTERY STIFFNESS

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Impedance is a complex and comprehensive function of hemodynamics that can be measured *in vivo* and from which certain metrics, including input impedance (Z_0), first harmonic impedance (Z_1) and characteristic impedance (Z_C), can be calculated. According to lumped-parameter models of intact human lungs, Z_1 is proportional to proximal artery (PA) stiffness and Z_C is directly proportional to PA stiffness and inversely proportional to size. Our goal was to investigate how these metrics of impedance are related to PA stiffness in isolated mouse lungs.
Sinusoidal pressure-flow tests in isolated lungs and static pressure-diameter tests in isolated PAs from inbred mice were performed after exposure to zero days (CTL) or ten days of hypoxia (HPH). To normalize mean PA pressure in isolated lungs, measurements were taken with and without vasodilation (Y27632, $1X10^{-5}$ M).
In PAs, the incremental elastic modulus (E_{inc}) increased with HPH ($P<0.05$); no differences in size were significant. In lungs, Z_1 increased ($P<0.0001$) but Z_C decreased ($P<0.05$) with HPH while mean PA pressure (and Z_0) increased ($P<0.0001$). When measured at the same pressure (and Z_0), Z_1 returned toward CTL values ($P=0.10$ vs. CTL) but Z_C remained decreased ($P<0.00001$). Under these conditions, PAs were still stiffer than CTL ($P<0.0005$) and slightly but not significantly larger ($P=0.051$).
Overall, Z_1 was sensitive to pressure-induced dilation and strain-stiffening in PAs but Z_C was additionally sensitive to HPH-induced stiffening. In contrast to intact human lungs, our results suggest that in isolated mouse lungs Z_C is inversely proportional to PA stiffness.

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P2.01
LONGITUDINAL STUDY OF VASCULAR MARKERS OF PREMATURE ATHEROSCLEROSIS IN PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Patients with pediatric Systemic Lupus Erythematosus (pSLE) are at increased risk of premature atherosclerosis irrespective of exposure to traditional cardiovascular risk factors. The goals of this study were to determine the progression of vascular markers of premature atherosclerosis in a prospectively followed pSLE cohort and the role of treatment and disease activity related factors.
Methods: At baseline and first follow-up drug therapy and disease activity were recorded, fasting lipid and glycemic profiles performed; and vascular markers including intima-media thickness (CIMT), flow-mediated dilatation (FMD), and pulse wave velocity (PWV) assessed. Differences between baseline and follow-up time points were tested as paired measures adjusted for time and compared in univariate analysis.
Results: Forty-three pSLE were assessed at baseline (age 14.0±2.8 years; disease duration 2.3±2.8 years, 81% female) and follow-up (1.6±0.5 years later). No overall difference was observed in CIMT (0.01±0.05 mm, $p=0.15$), FMD (0.19±5.0 %, $p=0.81$) and PWV (0.15±1.0 m/sec, $p=0.39$). When considering the time-dependent effects of treatment and disease activity on these vascular markers, corticosteroid use was found to be negatively associated with CIMT at follow-up ($r=-0.44$, $p=0.004$) and remained significant in a multiple variable model ($R2=0.63$, $p<0.001$).
Conclusion: In pSLE of relatively short duration, progression of vascular markers of premature atherosclerosis was not observed over short-term follow-up, but change in CIMT was found to be negatively associated with the amount of corticosteroid use. This suggests aggressive immunotherapy may reduce the atherogenic burden of chronic inflammation in pSLE and warrants further investigation.

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P2.02
IMPACT OF RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS ON ARTERIAL WALL STIFFNESS

A. Cypiene [1], A. Venalis [1], J. Dadoniene [1], R. Rugiene [1], L. Ryliskyte [2], Z. Petrulioniene [2], M. Kovaite [2], V. Skorniakov [2], A. Laucevicius [2].
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Background: There was demonstrated that rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) were associated with arterial damage. However it is not well known which of diseases has bigger impact on measures of arterial stiffness.
Aim of the study: was to assess whether aortic augmentation index (AIx) is modified in middle age RA and SLE women and to evaluate which one of these diseases has a greater influence on the parameter.
Methods: We examined 63 RA (age 41.48±10.77 years) with high disease activity (DAS28 5.49±0.92), 31 SLE (age 37.23±9.09) with moderate disease

activity (SLEDAI 18.74±8.25) and 72 controls (age 37.42±9.15) women. AIx was assessed non-invasively by applanation tonometry (Sphygmocor v.7.01, AtCor Medical).
Results: Using one-way ANOVA the overall difference of means of AIx between RA (24.71±11.52), SLE (20.81±12.29) and control groups (13.24±10.44); ($p<0.001$) was obtained. Post hoc tests revealed that AIx significantly differed between control group and each of disease groups ($p=0.006$ for SLE vs controls; $p<0.001$ for RA vs controls) however there was no difference between groups of SLE and RA ($p=0.253$). Adjustment for the other confounding factors, such as age, mean blood pressure, body mass index, fasting lipids and creatinine was made with a help of stepwise linear regression. However it did not change results. Variable indicating the presence of any of diseases was significant in the model for AIx ($p<0.001$).
Conclusions: RA and SLE are associated with increased arterial stiffness. The presence of both diseases contributes to increased augmentation index values and the damage of arterial wall.

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P2.03
EARLY INFLAMMATION CAN PREDICT ARTERIAL STIFFNESS: A 15-YEAR LONGITUDINAL STUDY OF 102 PATIENTS WITH RHEUMATOID ARTHTRITIS

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Objectives: To examine impact of early inflammation in RA on the development of CV disease.
Methods: 238 patients with RA of less than 4 years duration at inclusion in 1992 have been followed longitudinally. At the 15-year follow-up we performed Pulse wave analysis assessments including measurements of AI and PWV using the Sphygmocor apparatus (Atcor). The measurements were corrected for age, sex , MAP and heart rate. The AI was also corrected for height. Patients aged over 70 at the follow-up were omitted from the PWV analysis. Baseline measures of disease activity were then entered consecutively into the model.
Results: 102 patients were eligible for analysis of AI, 76 for PWV. Table 1 presents the adjusted univariate ß coefficients (CI)/p for the prediction of AI and PWV. In the multivariate model anti-CCP remained a significant predictor of AI $p=0.01$. R^2 adjusted increased from 0.43 to 0.46. In an alternative model without antiCCP, CRP remained a significant predictor $p=0.04$, R^2 adjusted 0.45. In the multivariate model CRP remained a significant predictor of PWV $p=0.02$. R^2 adjusted increased from 0.50 to 0.53.

Table1 Variable	AI (dependent variable)	PWV(dep. variable)
CRP	0.12 (0.00-0.25)/0.04	0.03(0.01-0.6)/0.02
ESR	0.06 (-0.008-0.14)/0.08	0.001 (-0.02-0.02)/0.93
IgMRF	0.02 (0.002-0.03)/0.03	0.002(-0.003-0.003)/0.89
Anti-CCP	0.02(0.004-0.03)/0.01	0.003(-0.003-0.003)/0.84
HAQ (health status)	1.67(-0.89-4.22)/0.20	0.46 (-0.05-0.99)/0.08
Sharp (radiographic)	0.09(-0.06-0.25)/0.23	-0.01 (-0.04-0.02)/0.60

Conclusion: Inflammation early in the disease course is associated with an increased augmentation index and pulse wave velocity after 15 years.

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P2.04
ASSOCIATION BETWEEN OSTEPONTIN AND ARTERIAL STIFFNESS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Aim: Osteopontin (OPN) is a pleiotropic cytokine involved in the regulation of mineralization, expressed in bone and kidney, whose levels are elevated during and inflammation. We evaluated the possible relationship between OPN and arterial stiffness in patients with rheumatoid arthritis (RA).
Methods: In 40 RA patients (56±5 years, 32 females) and 40 age and sex-matched healthy volunteers, applanation tonometry (Sphygmocor®) was applied for measuring augmentation index (AIx) and carotid to femoral pulse wave velocity (PWV). Endothelium-dependent (flow-mediated dilation, FMD) and independent (sublingual glycerol trinitrate, GTN, 25 μg) vasodilation were assessed by ultrasound and computerized analysis of brachial artery diameter changes. Plasma levels of OPN and C-reactive protein were also evaluated
Results: OPN levels resulted higher in RA patients than in healthy controls (13.3±9.8 vs 5.4±3.1 ng/ml; $p<0.05$). PWV (8.7±2.5 vs 7.6± m/s; $p<0.05$), AIx (30.8±8.3 vs 26.1±7.9 units; $p<0.05$) and FMD (6.1±.3.2 vs 7.2±3.2%; $p<0.05$) were significantly different in RA patients than controls In RA patients, log-transformed OPN was related to PWV($r=0.41$; $p<0.01$), but not to AIx, FMD or response to GTN. Log-OPN levels correlated significantly also with age ($r=0.37$; $P<0.01$), and log CRP ($r=0.31$; $p<0.05$). In multiple regression analysis ($r^2=0.35$) including age, mean blood pressure and logCRP, logOPN remained a significant predictor of aortic PWV ($p<0.05$).
Conclusions: RA patients are characterized by elevated OPN levels, increased arterial stiffness and endothelial dysfunction. The selective, independent relationship between OPN levels and aortic PWV suggests that OPN might represent an important marker/mechanisms for increased arterial stiffness in RA patients.

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P2.05
CENTRAL PULSE PRESSURE IN END-STAGE RENAL DISEASE: THE ROLE OF AORTIC DIAMETER, AORTIC STIFFNESS AND WAVE REFLECTION

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Objectives: To assess the determinants of central pulse pressure (CPP) in end stage renal disease (ESRD), with special focus on respective roles of wave reflection, aortic stiffness and geometry (diameter) compared with controls (CT).
Methodology: 115 ESRD (49±15 years, SBP/DBP: 152±3/82±1 mmHg) were compared to 59 CT without renal insufficiency (46±13 years (NS), 143±3 (<0.02)/87±2 mmHg (NS)). Cardiac echography (stroke volume (StVl), aortic diameter), carotid artery wave analysis, aortic wave reflections (tonometry) and aortic pulse wave velocity (PWV) were measured, with calculation of characteristic impedance (Zc, $dyne.s.cm^{-5}$). Multiple regression analyses were based on 2 models: M1: age, BP, cardiac function, AI% and Zc, and M2: age, BP, cardiac function, AI%, PWV and Aortic diameter (to assess determinants of Zc).
Results: Versus CT, ESRD had higher carotid pressures, heart rate, AI%, and PWV while aortic diameter was similar. Determinants of CPP in ESRD were age, MBP, cardiac StVl, AI% and Zc (M1 model: $R^2=0.70$, $p<0.001$), in CT: MBP, AI% and Zc ($R^2=0.67$, $p<0.001$). M2 model shows in ESRD: age, MBP, AI%, Aortic diameter and PWV ($R^2=0.61$, $p<0.001$). In CT, determinants were AI% and PWV ($R^2=0.46$, $p<0.001$) with no impact of aortic geometry.
Conclusion: Increased CPP is associated with increased arterial Zc and wave reflections. In controls, CPP is linked to stiffness and AI% only, and in ESRD: mainly stiffness and AI% plus minor impact of aortic geometry. In normal subjects and hypertensives without renal failure, CPP is determined by stiffness and reflection, but not by aortic geometry.

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P2.06
LEVELS OF NT-PROBNP ARE ASSOCIATED WITH ARTERIAL STIFFNESS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: We wished to investigate the association between arterial stiffness and NT-proBNP, a biomarker released in response to atrial and ventricular stretch (RA).
Methods: AI and PWV were measured using the Sphygmocor apparatus (Atcor) in 108 patients, 92 patients had acceptable AI, 95 patients acceptable PWV readings. The patients are included in the Euridiss register, an ongoing longitudinal study of Rheumatoid Arthritis (RA) disease activity. Cardiovascular end-points were assessed at the 2007 follow-up. AI and PWV were corrected for age, sex , MAP and heart rate and were dependent variables in separate models. AI was also corrected for height. Multivariate linear regression analysis with NT-proBNP as a continuous variable and ANOVA analysis with quartiles of NT-proBNP were performed.
Results: NT-proBNP was associated to PWV in the multivariate linear regression ß(CI) 0.024 (0.002-0.046) $p=0.03$. R^2 adjusted 0.57 R^2 change 0.02 $p=0.03$. The ANOVA analysis is shown below. NT-proBNP was not associated to AI ß(CI) 0.072 (-0.026-0.170) $p=0.15$.