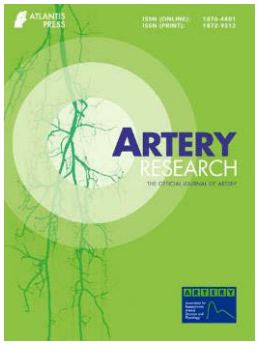

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P1.57: MODULATION OF ARGINASE IN RESPONSE TO WALL SHEAR STRESS

R.F. da Silva, V.C. Olivon, D. Segers, R. de Crom, R. Krams, N. Stergiopulos

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Methods: 132 normotensives (83 males, mean age 40.6 years) were divided in group A: non/light smokers (<5 pack-years, 67 subjects) and group B: heavy smokers (≥5 pack-years, 65 subjects). Augmentation index (AI) was measured using a validated device The A-to-G substitution was typed by Bbvl digestion of specific PCR products amplified from DNA.
Results: The two groups did not differ regarding sex, peripheral pressures, BMI and lipids (p=NS). Group A had lower AI than group B (16.5±12.5% vs 23.1±12.2%, p<0.01). In group A, the prevalence of AA vs AG+GG genotypes was 19.4% and 80.6; when compared to AA subjects, AG+GG subjects demonstrated higher levels of AI (AA:8.7±6.2% vs AG+GG: 18.4±13%; p=0.01). In group B, the prevalence of AA vs AG+GG was 29.2% and 70.8%; AI levels did not vary between the two subgroups (AA:24.3±11.3% vs AG+GG: 22.6±12.6%; p=NS).
Conclusion: In non/light smokers presence of the G allele accounts for deteriorated arterial elastic properties. This is not the case in heavy smokers, as wave reflections are equally impaired irrespectively of the G allele presence. These findings underscore the need for further research into the interplay between intrinsic, extrinsic oxidative stress and arterial function.

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P1.54
THE RELATIONSHIP OF THE INSULIN-LIKE GROWTH FACTOR (IGF) SYSTEM TO CARDIOVASCULAR STRUCTURE AND FUNCTION IN WOMEN

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Introduction: IGF-I and its binding proteins (BP) may modulate cardiovascular risk, from young ages. We examined relationships of IGF system indices (IGF-I, -BP-1, BP-3, IGF-I/BP-3 ratio) to cardiac and vascular structure & function across the whole vascular bed.
Methods: 193 women in our Manchester Mothers' Cardiovascular (CVS) study followed from an index pregnancy aged 32±5y had fasting blood samples, anthropometry, echocardiography, aortic pulse wave velocity and heat augmented laser doppler flowmetry (LDF). In a smaller subgroup (n=29), subcutaneous small artery structure and function was assessed *ex-vivo* by wire myography. IGF-I and IGFBP-3 were assayed by Elisa, and IGFBP-1 by radio-immunoassay.
Results: On multiple regression analysis, adjusting for age, ethnicity, smoking history, BMI, systolic blood pressure, fasting glucose, total cholesterol and triglycerides, IGF-I, IGFBP1 and the IGF-I/BP-3 ratio were independently related to CVS parameters as follows:

CVS parameter	IGF system	Beta	95% CI of Beta	p
LV Posterior Wall thickness	IGF-I/BP-3 ratio	−0.005	-0.009 to 0.00	0.04
Proximal aortic distensibility (echo)	IGF-I/BP-3 ratio	−0.014	-0.028 to 0.00	0.05
Heat augmented microcirculatory flow (LDF)	IGF-I/BP-3 ratio	0.05	0.007 to 0.094	0.03
	Ln IGFBP1	−0.66	-1.09 to -0.22	0.004
Subcutaneous small artery media: lumen ratio(n=29)	Total IGF-I	0.19	0.07 to 0.31	0.003
	IGF-I/BP-3 ratio	2.09	1.54 to 2.63	<0.001
	Ln IGFBP1	−28.0	-44.85 to -11.17	0.002

Conclusion: In relatively young women, higher concentrations of IGF-I, 'free' IGF-I (= IGF-I/BP-3 ratio) and of IGFBP-1 had marked influences on cardiac, large and small vessel structure and function.

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P1.55
INFLUENCE OF THE SOLUBLE CD14 ON AORTIC STIFFNESS USING A MENDELIAN RANDOMIZATION

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Background: CD14 receptor is at the crossroads between infection and inflammation. Present on the myeloid cell surface, it binds lipopolysaccharides and induces a release of cytokines whose deleterious effects on the arterial wall have been documented. Present as soluble protein (sCD14), its blood concentration increases in response to bacterial invasion and partly inhibits response to lipopolysaccharide of macrophages. In humans, soluble CD14 has been associated with aortic stfffness.
Objective: The aim of this study was to analyse in a large population-based sample the relationship of sCD14 with aortic stiffness using a Mendelian randomization approach.
Methods: 1015 subjects randomly selected from the polling lists, were recruited by the Toulouse MONICA center. After fasting, blood sample was drawn, blood pressure and carotid femoral pulse wave velocity were successively measured in supine position. sCD14 was measured using an immunoenzymatic method. A genotypic examination for the CD14 C260T polymorphism was performed.
Results: An increase in sCD14 expression was observed in subjects carrying t allele (p<0.001). No significant difference in intima-media thickness, number of plaques and pulse wave velocity was noticed according to C260T polymorphism. An interaction was observed between C260T polymorphism and current smoking in sCD14 expression: among smokers, no significant change in sCD14 was observed in individuals carrying t allele.

*adjusted for age and risk factors	CC	CT	TT	p	p*
	N=218	N=433	N=235		
sCD14 (mg/ml)	3.36 ± 1.02	3.56 ± 1.06	3.66 ± 0.97	0.008	0.003
PWV m/s	8.95 ± 1.65	8.96 ± 1.73	9.01 ± 1.71	0.45	-

Conclusion: This large population—based study does not support the causative nature of the link observed between soluble CD14 and aortic stiffness.

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P1.56
DETERMINANTS OF AORTIC STIFFENING IN DIABETES: THE INFLUENCE OF COLLAGEN TURNOVER, AUTONOMIC DYSFUNCTION, AND SYSTEMIC INFLAMMATION

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Although aortic stiffening is a strong predictor of cardiovascular mortality in diabetes, the underlying mechanisms have yet to be fully determined. In this cross-sectional study, we investigated determinants of aortic stiffness (aortic pulse wave velocity (PWV)) by measuring systemic collagen formation and turnover (plasma concentrations of procollagen type 1 N-propeptide (plasma P1NP)), cardiovascular autonomic function and systemic inflammation (hsCRP), in subjects with type 1 and 2 diabetes, in comparison with impaired glucose tolerance (IGT) subjects.
Fifty males with diabetes (35 type 2, 15 type 1) (age range 39-75yrs) and 21 males with IGT (age range 42-69yrs) were studied. Concentrations of P1NP were higher in type 1 in comparison with type 2 and IGT subjects (40.3±18.3 ug/L versus 28.1±12.5 ug/L versus 30.4±9.8 ug/L respectively, p<0.05) and were positively correlated with aortic PWV in type 1 (r=0.56, p<0.05) and type 2 subjects (r=0.46, p<0.01). Multiple regression analysis revealed age, hsCRP and P1NP to be stronger predictors of aortic PWV in diabetic subjects in comparison with other measured cardiovascular risk factors including autonomic dysfunction.
Our findings highlight the likely importance of increased collagen turnover as a predictor of aortic stiffening in diabetes. P1NP concentration was more strongly predictive of aortic stiffening than conventional risk factors with the exception of age. Further investigation is required to establish whether true differences in collagen turnover exist between type 1 and 2 diabetes.

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P1.57
MODULATION OF ARGINASE IN RESPONSE TO WALL SHEAR STRESS

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Introduction: Aterations of wall shear stress can predispose the endothelium to the development of atherosclerotic plaques. Ample evidence indicates that arginase expression/activity correlates with several risk factors for cardiovascular disease including atherosclerosis. However, the

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

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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