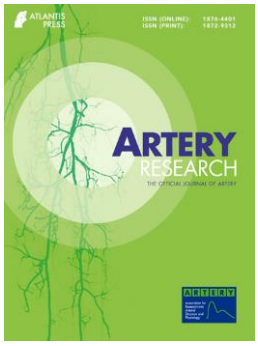

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P5.01: PRE-PREGNANCY TO EARLY PREGNANCY CHANGES IN MATERNAL CARDIOVASCULAR PHYSIOLOGY

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P4.10
THE SEMICARBAZIDE-SENSITIVE AMINE OXIDASE (SSAO): A NEW ACTOR IN ATHEROSCLEROSIS IN THE APOE MOUSE MODEL?

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The expression of « semicarbazide sensitive amine oxidase » (SSAO), an enzyme which transforms primary amines into aldehydes, ammonia and hydrogen peroxide, increases during smooth muscle cell differentiation (VSMC) and is widely expressed in the media layer from the arterial wall. The SSAO has been implicated in LDL oxidation and in inflammation. We hypothesized that the absence of SSAO should prevent the development of atherosclerosis. The progression of the disease and the implicated mechanisms were studied in double ApoE/SSAO knock out mice (ApoE-/-SSAO-/-) established in the laboratory.
Surprisingly 25 week-old ApoE-/-SSAO-/- mice presented a significant 50 % increase in plaque surface associated with an 80% decrease in a-actin expression in the media of aortic sinus from ApoE-/-SSAO-/- mice compared to ApoE-/- mice. We noticed a small T-cell infiltration in the media from ApoE-/-SSAO-/- mice whereas no T-cell infiltration was observed in the media from ApoE-/- mice. No difference was detected in monocytes/macrophages infiltration in the plaque in aortic sinus from APOE-/-SSAO-/- mice and ApoE-/-. The pro- (TNFa and INFg) and anti-inflammatory (IL10 and TGFb) cytokine expressions were similar in the spleen from ApoE-/- and ApoE-/-SSAO-/- measured at 25 and 15 week old.
In conclusion, the absence of the SSAO increases the atherosclerosis in ApoE-/- mice. This result could be explained either by a modification of VSMC phenotype or to an increase in VSMC apoptosis in inflammatory situation. Thus, the SSAO could be a new potential actor implicated in the inhibition of atherosclerosis development.

P4.11
GALECTIN-3 IS A POTENTIAL MEDIATOR OF ALDOSTERONE EFFECTS IN VASCULAR REMODELING

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Background. Aldosterone (Aldo) plays a major role in extracellular matrix (ECM) remodeling leading to heart failure (HF), but the mechanisms remained unclear. Galectin-3 (Gal-3), a β-galactosidase-binding lectin, plays an important role in inflammation and HF. We investigated whether Gal-3 mediates Aldo-induced ECM remodeling in vascular smooth muscle cells (VSMCs) *in vitro* and *in vivo*.
Methods. *In vitro*, primary cultured VSMCs were stimulated with Aldo (10^{-8}M) for 24h, with or without mineralocorticoid receptor (MR) antagonist. Gal-3 was over-expressed (transfection) and knocked-down (siRNA). Gal-3 expression and ECM production were evaluated by RT-PCR, Western blot and immunohistochemistry. *In vivo*, Wistar rats were treated by Aldo (1mg/kg/day)+salt or Aldo+salt+spironolactone (200mg/kg/day) for 3 weeks. Gal-3 and ECM proteins (collagen type I and III, fibronectin and elastin) were quantified by Western Blot and immunohistochemistry, and metalloproteinase (MMP) activities by zymography.
Results. *In vitro*, VSMCs spontaneously expressed Gal-3. Gal-3 over-expression enhanced ECM synthesis. Aldo up-regulated Gal-3 and ECM protein expression via MR. The Gal-3 silencing blocked Aldo-induced ECM production by VSMCs. In Aldo-salt hypertensive rats, Gal-3 aortic expression, ECM proteins and MMP activities were enhanced. Spironolactone treatment reversed all the above effects. Aortic Gal-3 expression was positively correlated with collagen type I, elastin, MMP-2 and MMP-13 activity.
Conclusions. Gal-3 is spontaneously expressed by VSMCs and induces ECM synthesis. It mediates Aldo-induced ECM remodeling via MR activation *in vitro* and *in vivo*. Our data suggest a key role for Gal-3 in Aldo-induced vascular alterations.

P4.12
MODEL BASED ESTIMATION OF AORTIC PULSE WAVE VELOCITY

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The proposed model is inspired by the theoretical frameworks of (1) Moens-Korteweg, (2) Bramwell & Hill, (3) Waterhammer equation used in ARCSolver. All of the mentioned equations allow the determination of velocity in an elastic tube from a single point measurement. Whereby Moens-Korteweg consider the tension of the wall and the radius of the vessel as well as the viscosity of blood which can be assumed constant and near one in the human circulation for simplicity. It's now not really surprising that with increasing pressure both wall tension and wall radius will elevate. In younger age both parameters likely to the same extent and with only minor effects on PWV. With increasing age distensibility of the arterial wall degenerates. Subsequently an increase in pressure will not be compensated by a diameter change, even more tension within the wall will increase and PWV as well. All changes affect PWV non linear. Equation 2 rewrites equation 1 to consider observable variables like pressure and volume flow. Simply spoken, PWV is a result of pressure changes and volume displacement. In complex transmission line theory using Fourier analysis, the relation between arterial flow and blood pressure is described by the so called characteristic impedance (Zc) illustrated in the Waterhammer Equation (3). ARCSolver calculates (Zc) using an adopted Windkessel model. Determinants of ARCSolver-PWV are wall tension (impedance), aortic blood pressure and age.

P4.13
RELATION OF AORTIC AUGMENTATION INDEX TO ARTERIAL AND VENTRICULAR PROPERTIES

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Aortic augmentation index, the amount by which aortic pressure is "augmented" above the first systolic shoulder of the aortic pulse wave, expressed as a ratio of aortic pulse pressure, is thought to relate to arterial properties. In particular it has been cited as an index of "arterial wave reflection" related to arterial stiffness. However, it could also be influenced by the characteristics of ventricular ejection. The objective of the present study was to examine the relation of AIx to arterial stiffness and ventricular contraction-relaxation. We studied 74 asymptomatic subjects, aged 24-89 years, 7-15 subjects per decade) using an Aloka α10 ultrasound system with 3MHz cardiac probe to perform conventional echocardiography, obtain tissue Doppler ventricular velocities and mitral flow velocities. Using the same system with a 10MHz linear vascular transducer, ECG-referenced echo-tracking of the carotid and femoral arteries was used to obtain carotid augmentation index (AIx) and carotid-femoral pulse wave velocity (PWV). The relation of AIx to PWV and ventricular tissue velocities was examined using univariable and multivariable regression analysis. On multivariable analysis, entering age, mean arterial blood pressure and all measures correlated with AIx on univariable analysis (including PWV), AIx was independently negatively correlated only with heart rate and the ratio of diastolic to atrial mitral valve flow velocities (E/A). Together these variables explained 39% of the variability in AIx. These results suggest that AIx is more closely related to ventricular contraction-relaxation than to arterial properties.

P5 — Clinical Science 1

P5.01
PRE-PREGNANCY TO EARLY PREGNANCY CHANGES IN MATERNAL CARDIOVASCULAR PHYSIOLOGY

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Maternal heart rate, blood pressure and cardiac output change as early as 5-6weeks in pregnancy. However, most of the longitudinal studies assessing maternal haemodynamic adaptation have used late first trimester

measurements as 'baseline' against which changes in normal and complicated pregnancies have been compared. Moreover, the extent of changes in maternal arterial stiffness and central haemodynamics very early in pregnancy is not known.
Our aim was to assess pre-pregnancy to early pregnancy maternal cardiovascular adaptation including arterial stiffness.
Method: 44 women planning to conceive were prospectively recruited (22-40yrs). Cardiovascular assessments were performed pre-pregnancy and repeated very early in pregnancy (2-3 weeks after the first positive pregnancy test) including brachial and central blood pressures, augmentation index (AIx), aortic pulse wave velocity (aPWV) and cardiac output (CO).
Results: While heart rate ($P=0.001$) and cardiac output ($P=0.005$) increased significantly, both brachial and central blood pressure were significantly reduced ($P<0.001$) within 2-3 weeks of conception. AIx was also significantly reduced, even after adjustment for the change in HR ($P=0.005$) along with a reduction in peripheral vascular resistance ($P=0.008$). aPWV was unaltered, even after adjustment for MAP ($P=0.6$).
Conclusion: This is the first study to investigate changes in AIx and PWV very early in pregnancy. We have demonstrated profound changes in brachial and central blood pressures and AIx within 2-3 weeks of conception, with no change in aPWV. Furthermore, late first trimester data cannot be used as 'baseline' data in order to identify the extent of cardiovascular adaptation in pregnancy as has been hitherto assumed.

Table 1 Pre-pregnancy to early pregnancy (2-3 weeks after positive pregnancy test) cardiovascular changes

	Pre-pregnancy	Early pregnancy	$P*$
HR (beats/min)	69 ± 11	73 ± 10	0.001
Brachial SBP (mm Hg)	108 ± 9	103 ± 7	<0.001
Brachial DBP (mm Hg)	70 ± 7	64 ± 5	<0.001
MAP (mm Hg)	84 ± 8	77 ± 5	<0.001
CSBP (mm Hg)	98 ± 9	91 ± 6	<0.001
CO (L/min)	5.5 ± 1.0	5.9 ± 1.1	0.005
SV (ml)	76 ± 10	77 ± 14	0.6
CI (L/min/m^2)	3.2 ± 0.6	3.5 ± 0.6	0.003
PVR (dynes.s^{-1}.cm^{-5})	1253 ± 253	1074 ± 223	0.008
Supine AIx_a (%)	20 ± 9	13 ± 9	<0.001
Supine AIx_b (%)	19 ± 10	13 ± 9	0.005
$aPWV_a$ (m/sec)	5.2 ± 0.6	5.0 ± 0.5	0.1
$aPWV_c$ (m/sec)	5.1 ± 0.5	5.2 ± 0.5	0.6

Data are means ± SD. a= unadjusted. b= heart rate adjusted. c=adjusted for Mean arterial pressure.
*$P<0.05$ is statistically significant
(Heart rate= HR, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, MAP=Mean arterial pressure, CSBP= Central systolic blood pressure, CO=cardiac output, SV= stroke volume, CI= Cardiac Index, PVR= peripheral vascular resistance)

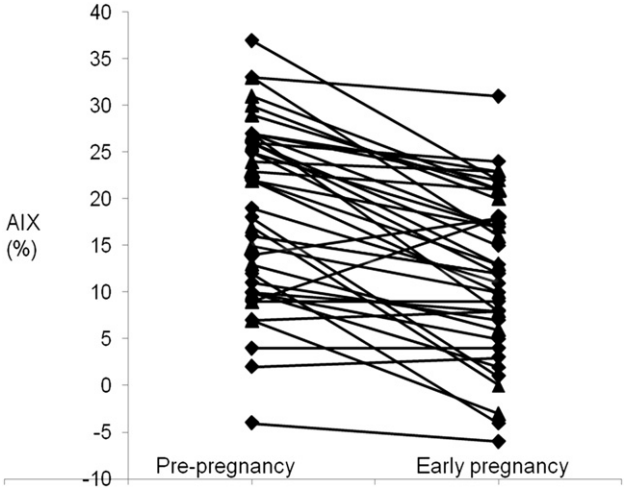

Figure 1 Pre-pregnancy to early pregnancy changes in AIx (%)

P5.02
FREQUENT AND WIDESPREAD VASCULAR ABNORMALITIES IN HUMAN STAT3 DEFICIENCY

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Background: STAT3 deficiency is responsible for autosomal dominant hyper-IgE syndrome characterized by recurrent bacterial and fungal infections, connective tissue abnormalities, hyper-IgE and Th17 lymphopenia. Although vascular abnormalities have been reported in some patients, the prevalence, characteristics and etiology of these features have yet to be described.
Methods We prospectively screened 21 adult STAT3-deficient patients (median age: 26; range 17 - 44) for vascular abnormalities. They were explored with whole-body magnetic resonance imaging angiography, coronary multislice computed tomography and echotracking-based imaging of the carotid arteries. We also assayed for serum biomarkers of inflammation and endothelial dysfunction. Finally, murine models of aortic aneurysm were studied in the presence and absence of inhibitors of STAT3-dependent signaling.
Results: Brain abnormalities (white matter hyperintensities, lacunar lesions suggestive of ischemic infarcts, atrophy) were found in 95% of patients. Peripheral and brain artery abnormalities were reported in 84% of patients, whereas coronary artery abnormalities were detected in 50%. The most frequent vascular abnormalities were ectasia and aneurysm. The carotid intima-media thickness was markedly decreased, with a substantial increase in circumferential wall stress indicating the occurrence of hypotrophic arterial remodeling in this STAT3-deficient population. Systemic inflammatory biomarker levels correlated poorly with the vascular phenotype. In vivo inhibition of STAT3 signaling or blockade of IL-17A resulted in a marked increase in aneurysm severity and fatal rupture in mouse models.
Conclusions Vascular abnormalities are highly prevalent in STAT3-deficient patients. This feature is consistent with the greater susceptibility to vascular aneurysm observed after inhibition of STAT3-dependent signaling in mouse models.

P5.03
THE CENTRAL HEMODYNAMIC RESPONSE TO POSTURAL STRESS IS UNFAVOURABLY ALTERED IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background. An abnormal brachial BP response to postural stress is associated with increased risk of developing hypertension and stroke. However, the hemodynamic responses contributing to changes in central BP with postural stress are not well characterised, and we aimed to determine these in healthy controls (HC) and patients with type 2 diabetes (T2DM); in whom we hypothesised would have an abnormal postural response..
Methods. 20 HC (53±8yrs,45% male) and 21 T2DM (61±9yrs,48% male) patients underwent measurement of central BP (by radial tonometry), with simultaneous bioimpedance cardiography to determine stroke volume (SV) and cardiac output (CO), in seated and standing postures. Systemic vascular resistance (SVR; mean arterial pressure/CO), and arterial elastance (E_A; end systolic pressure/SV) were calculated. Postural changes were defined as seated minus standing values.
Results. Central pulse pressure (PP) was higher in patients with T2DM and did not significantly change from the seated-to-standing positions ($P=0.461$), whereas there was a significant decrease upon standing in HC ($P=0.022$). The change in central SBP correlated with the change in SVR and E_A in HC ($r=0.67$, $P=0.002$ and 0.68, $P=0.001$ respectively), but not in patients with T2DM ($r=-0.05$, $P=0.790$ and $r=0.03$, $P=0.910$ respectively). SV was the only significant correlate of change in central systolic BP in patients with T2DM ($r=0.62$, $P=0.004$), and this was not observed in HC ($r=-0.08$ $P=0.760$).
Conclusions. Central hemodynamic responses to postural stress are altered in patients with T2DM and result in persistent elevation of central PP while standing. This may contribute to increased cardiovascular risk associated with T2DM.