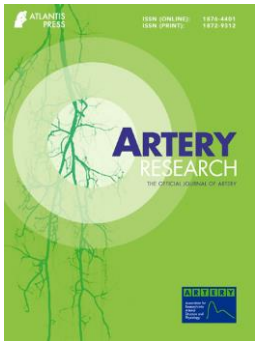

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P5.21: CHRONIC HYPOXEMIA PER SE INDUCES SYSTEMIC VASCULAR DYSFUNCTION IN HUMANS

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P5.18
BRONCHOCONSTRICTION DOES NOT SIGNIFICANTLY ALTER CENTRAL HAEMODYNAMICS IN HEALTHY YOUNG ADULTS

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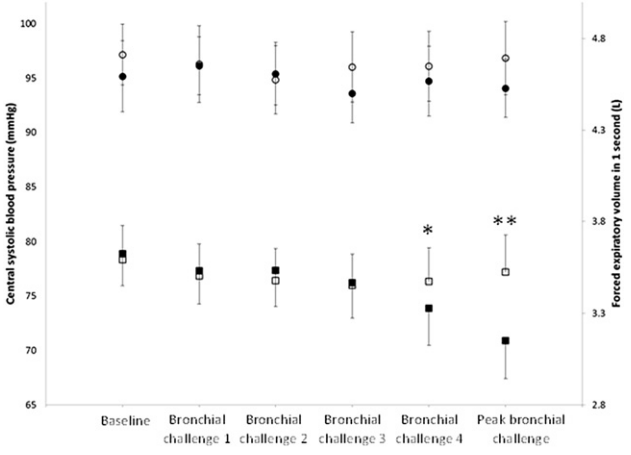
Background: Cardiovascular disease is the most frequent cause of death in people with chronic respiratory disease. Whether this association is due to shared comorbidities or adverse respiratory function exerting detrimental cardiovascular effects is unknown. This study aimed to determine the cardiovascular effect of methacholine-induced acute airway obstruction.
Methods: Fifteen healthy young adults (aged 22.9±2.5 years; 4 male; mean±SD) underwent a bronchial challenge test in which they were randomized in a blinded cross-over design to receive nebulized methacholine inhalation in serially increasing concentrations (from 0.39 to 25 mg/ml) or saline (0.9%; control) on two separate days. Airflow obstruction was assessed by forced expiratory volume at second (FEV1) and cardiovascular effects by brachial BP (oscillometry), central BP, augmentation index (AIx) and aortic stiffness (applanation tonometry).
Results: Methacholine caused a significant decrease in FEV1 (bronchoconstriction) from baseline to peak inhalation compared with saline (-0.48±0.34 vs -0.07±0.16 L; $p<0.001$), but no significant between-group change in aortic stiffness (0.2±1.3 vs 0.8±1.8 m/s; $p=0.20$), AIx (1.6±7.0 vs 3.7±10.2%; $p=0.49$), brachial SBP (-3.3±7.6 vs -4.7±5.7 mmHg; $p=0.59$), central SBP (-1.1±5.2 vs -0.3±5.5 mmHg; $p=0.73$), or heart rate (0.4±7.1 vs -0.8±6.6 bpm; $p=0.45$). See figure for FEV1 and central SBP responses to inhaled methacholine (*$P=0.012$, **$P<0.0001$).
Conclusions: Methacholine-induced bronchoconstriction does not change cardiovascular function, as assessed by aortic stiffness, brachial and central BP in healthy young adults. A comparison of the responses in people with airway disease would be of interest and may help to elucidate the connection between cardiovascular and respiratory disease.



P5.19
MATERNAL HEMODYNAMICS AT 11−13 WEEKS OF GESTATION AND THE RISK OF PRE-ECLAMPSIA

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Background: Women who develop preeclampsia (PE) are at increased risk of cardiovascular disease and stroke in the subsequent decades. In individuals with cardiovascular disorders there is increased central aortic systolic blood pressure (SBP_{Ao}) and arterial stiffness, assessed by pulse wave velocity (PWV) and augmentation index (AIx). The aim of this screening study was to examine the potential value of assessment of $SBP_{Ao,}$ PWV and AIx at 11-13 weeks' gestation in identifying women who subsequently develop PE.
Methods: This was a screening study for PE in singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation. Maternal history and characteristics were recorded and PWV, AIx and SBP_{Ao} were measured by the Arteriograph. We compared these parameters in those that developed PE (n=146) with unaffected controls (n=4,436) and examined their performance in screening for PE.
Results: In the PE group, compared to unaffected controls, there was an increase in PWV (1.12 vs 1.00 MoM, $p<0.0001$), AIx-75 (1.06 vs 1.00 MoM, $p<0.0001$) and SBP_{Ao} (1.10 vs. 1.00 MoM, $p<0.0001$). In screening for PE by a combination of maternal variables and $\log_{10}$ AIx-75 MoM, $\log_{10}$ PWV MoM and $\log_{10}$ SBP_{Ao}, the estimated detection rate was 61.6 (95% CI 51.8-70.5), at a false-positive rate of 10%.
Conclusion: A high proportion of women who develop PE have increased SBP_{Ao} and arterial stiffness that is apparent from the first-trimester of pregnancy.

P5.20
ADDITIVE EFFECT OF CARDIOVASCULAR RISK FACTORS ON CAROTID AND AORTIC STIFFNESS IN ESSENTIAL HYPERTENSIVE PATIENTS

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Background: The role of other cardiovascular risk factors (RF) on top of hypertension in worsening arterial elastic properties is still unknown. The aim of the study was to evaluate whether cardiovascular RF can influence aortic and carotid stiffness in essential hypertensive patients.
Methods: 314 hypertensive patients and 110 age- and sex-matched healthy subjects were recruited. Carotid-to-femoral PWV and carotid pulse pressure were obtained by applanation tonometry, and carotid stiffness (CS) by automated system for ultrasound sequence images "Carotid Studio". Medical history, physical examination, and blood exams were used to identify the following RF: family history of premature cardiovascular disease, smoking, previous cardiovascular events, diabetes mellitus, obesity, hypercholesterolemia, hypertriglyceridemia, low HDL, metabolic syndrome, and chronic renal failure.
Results: Hypertensive patients had higher PWV and CS compared to healthy subjects (9.4 vs 7.4 m/s and 6.9 vs 6.2 m/s, $p<0.0001$ for both). PWV and CS were classified as "increased" when greater than 90^{th} percentile, calculated on the healthy subjects sample. Among hypertensives, age- and sex-adjusted multiple logistic regression, including all the above-mentioned RF, demonstrated that only diabetes mellitus (OR 5.4, CL95% 2.6-11.2) and chronic renal failure (OR 7.7, CL95% 2.2-25.6) are independently associated to an increased PWV while only diabetes mellitus is independently associated to an increased CS (OR 3.2, CL95% 1.4-7.1).
Conclusions: In hypertensive population, the additive presence of diabetes mellitus is associated with a further carotid and aortic stiffening, while the presence of chronic renal failure is associated to a further increased PWV. The other cardiovascular RF seem to exert a marginal role, when added to arterial hypertension.

P5.21
CHRONIC HYPOXEMIA PER SE INDUCES SYSTEMIC VASCULAR DYSFUNCTION IN HUMANS

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Cardiovascular (CV) morbidity and mortality are increased in patients suffering from diseases associated with chronic hypoxemia. The contribution of hypoxemia per se has proven difficult to determine, because these patients often present several additional CV risk factors. Chronic mountain sickness (CMS) is characterized by chronic hypoxemia, affects subjects with a low CV risk profile and thereby provides a unique opportunity to study the independent effects of chronic hypoxemia on vascular function. We measured arterial oxygen saturation (SaO_2), flow-mediated dilation (FMD) of the brachial artery, carotid-femoral pulse wave velocity (PWV) and carotid intima-media thickness (IMT) in 23 CMS patients and 27 controls permanently living at 3600 m. The main new finding was that CMS patients (SaO_2 83±3 vs. 90±3% in controls, $P<0.0001$) displayed marked systemic vascular dysfunction as evidenced by decreased FMD (4.6±1.2 vs.

7.6±1.9%, P<0.0001) and increased PWV (10.6±2.1 vs. 8.4±1.0 m/s, P<0.001) and IMT (690±120 vs. 570±110 μm, P=0.001). Oxygen administration almost completely restored FMD in CMS patients but had no effect in controls. These data demonstrate for the first time that chronic hypoxemia per se induces systemic vascular dysfunction in humans. We speculate that improving arterial oxygenation per se has favorable effects on CV morbidity and mortality in chronically hypoxemic patients.

P5.22
CAROTID AND AORTIC STIFFNESS IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

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Aim: The role of plasma cholesterol in impairing arterial function and elasticity remains not completely defined. We evaluated the arterial stiffness, measured locally in the common carotid artery with a high-precision echotracking, and aortic stiffness, measured with carotid-femoral pulse wave velocity (PWV) (the «gold-standard» measurement of arterial stiffness), in patients with never-treated heterozygous familial hypercholesterolemia (FH).
Subjects and methods: The study included 66 FH patients aged 10-66 years (38 (27-48) years) and 57 their first-degree relatives without FH aged 11-61 years (33 (23-42) years). Carotid-femoral PWV was determined by SphygmoCor (AtCor, Australia). The parameters of carotid stiffness β-index, Peterson elastic modulus (Ep) and local PWV were assessed at the common carotid artery 1cm before the bifurcation (Aloka Prosound Alpha7, Japan). Data are represented as median (25th-75th percentile).
Results: There were no differences in age, sex, high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), fibrinogen, lipoprotein(a) (Lp(a)), homocysteine, cases of hypertension. The FH patients had significantly elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), body mass index (BMI), frequency of tendon xanthomas, and coronary artery disease (CAD).
FH patients had significantly higher β-index (6,3(4,8-8,2) vs. 5,2(4,2-6,4), p=0,005), Ep (78(53-111)kPa vs. 62(48-79)kPa, p=0,006), local PWV (5,4(4,5-6,4)m/c vs. 4,7(4,2-5,4)m/c, p=0,005), but the same values of carotid-femoral PWV (6,76(7,0-7,92)m/c vs. 6,48(6,16-7,12)m/c, p=0,138).
Conclusions: Compared with their relatives, never-treated FH patients had stiffer carotid arteries but no differences in aortic stiffness.
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P5.23
TIMP1 PLASMA LEVELS ARE CORRELATED WITH ARTERIAL STIFFENING PROCESS

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Introduction: Arterial stiffness and left ventricle hypertrophy are associated with a decrease in collagen type1 degradation. Aim of our study was to address whether an increase in plasma levels of metalloproteinases-1 (MMP1, responsible for collagen type1 degradation) and her tissue inhibitor (TIMP1) are correlated to the presence of subclinical vascular organ damage (VOD) as defined by ESH-ESC Hypertension guidelines.
Methods: In 251 well-treated hypertensive outpatients (HT, age 57±12.5 years, Blood Pressure,BP,132±18/79±11mmHg mean±SD) we assessed carotido-femoral PWV (Complior) and we measured serum levels of MMP-1 and TIMP-1 (ELISA). Patients were divided in two groups, the first group including those with PWV<12m/sec (NOD) and the second one including patients with PWV ≥12m/sec, indicative of VOD.
Results: 93 patients showed VOD (37%), and 151 NOD (60%). VOD subjects were older than NOD (63±10vs53±12 years, p<0.001), had higher Systolic BP values (141±20 vs. 127±15mmHg, p<0.001) and higher TIMP1 plasma levels (162.27±46.3vs141.98±39.0, p<0,01), while there were no differences in MMP1. Furthermore in the whole population we found a correlation between PWV and TIMP1 (p=0.04, r=0,19), the correlation survived after adjusting for SBP but disappeared adjusting for age.
Discussion: In our study, HT patients with VOD were older and had higher SBP compared with NOD, they had also higher serum levels of TIMP1. Therefore TIMP1 plasma levels might be a further indicator of the cardiovascular aging process that is the first responsible of arterial stiffening.

P5.24
PULMONARY ARTERIAL HYPERTENSION AND ARTERIAL STIFFNESS

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Background: Endothelium plays an important role in the development and progression of Pulmonary Arterial Hypertension (PAH), independently of its aetiology. Little is known on derived central blood pressure (CBP) and arterial stiffness in PAH. The aim of this study was to describe CBP and arterial stiffness as measured by PWA (Aix).
Methods: We studied 21 PAH patients; 11 were first diagnosis and not treated (PAHNT, age 58±17 yrs, BP 135±33/81±16 mmHg, direct PAPc 49±13 mmHg mean±SD); 10 were under specific drugs (Calcium channel blockers, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin derivatives) (PAHT, age 67±8 yrs, BP: 136±28/72 ±14 mmHg, PAPc, 42±14mmHg). 10 age and sex matched subjects served as controls (C, age 61±15 yrs, BP:130±13/77±6 mmHg). We used applanation tonometry (Sphygmocor, AtCor) to study PWA and to derive CBP and Aix, which was used as an index of arterial stiffness.
Results: Both systolic and diastolic CBP were similar in the three groups. On the contrary Aix was higher in PAH than in C (26 ± 7.8 vs. 19 ±11.6%); among the two PAH groups, Aix was significantly higher in NT than in T (30±6.9 vs. 22±7.1% p<0.02). In PAH Aix showed significant correlation (p<0.05) only with BMI (r=-0.49).
Conclusions: Our data show that AIx is increased in PAH. They also show that it decreases in association with specific therapy. This pilot study suggests that AIx could be used in PAH as an additional non-invasive marker to assess the efficacy of therapy.

P5.25
CENTRAL PULSE PRESSURE AND AORTIC STIFFNESS DETERMINE RENAL ARTERY FLOW: HEMODYNAMIC MECHANISM PROPOSED FOR MICROALBUMINURIA

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A significant link has been shown between aortic stiffening and renal microvascular damage, but the underlying mechanism is not fully understood. We hypothesized that alterations in central and renal hemodynamics are responsible for this link. In 133 patients with hypertension, pressure waveforms were recorded on the radial, carotid, femoral and dorsalis pedis arteries with applanation tonometry to estimate the aortic pressures and aortic (carotid-femoral) and peripheral (carotid-radial and femoral-dorsalis pedis) pulse wave velocities (PWVs). Flow-velocity waveforms were recorded on the renal segmental arteries with duplex ultrasound to calculate the resistive index (RI) as [1 − (end-diastolic velocity/peak systolic velocity)], and on the femoral arteries to calculate the reverse/forward flow index and diastolic/systolic forward-flow ratio. (Micro)albuminuria was defined as urinary albumin/creatinine ratio (UACR) ≥30mg/gCr. The renal RI (mean, 0.65±0.07) was strongly correlated ($P<0.001$) with the aortic pulse pressure ($r=0.62$), incident pressure wave ($r=0.55$), augmented pressure ($r=0.52$) and aortic PWV ($r=0.51$), though not with the mean arterial pressure or peripheral PWVs. The correlations remained highly significant after adjustment for confounders including age, sex, hypercholesterolemia, diabetes and serum creatinine. The renal RI was inversely correlated with the femoral reverse and diastolic forward flow indices. Both aortic pulse pressure and renal RI correlated with UACR independently of the confounders. Each 0.1 increase in renal RI was associated with a 4.6-fold increase in the adjusted relative risk of (micro)albuminuria. In conclusion, increased aortic pulse pressure due to aortic stiffening causes renal microvascular damage through altered renal hemodynamics resulting from increased peripheral resistance and/or increased flow pulsation.