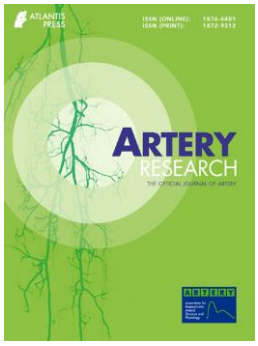

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P1.53: INTRINSIC VERSUS EXTRINSIC OXIDATIVE STRESS AND THEIR IMPACT ON ARTERIAL ELASTIC PROPERTIES: THE ROLE OF NADPH OXIDASE AND SMOKING ON WAVE REFLECTIONS AND AORTIC PRESSURES

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(TOD)may increase the number of patients classified at high CV risk.The aim of our study was to assess the effect of the evaluation of different forms of TOD,in addition to ''routine'' work-up,on CV risk(CVR)stratification in a general population.
Methods:In 385 untreated subjects(age 57±10 years,44% males,64% hypertensives(HT),32% treated)left ventricular and carotid artery structure and carotido-femoral PWV were measured. All subjects underwent laboratory examinations.Subjects were divided into risk categories according to ESH/ESC guidelines before and after TOD evaluation.
Results: After routine work up patients were classified as follows:7% at average CVR,35% at low CVR,26% at moderate CVR,31 at high CVR and 1% at very high CVR.The proportion of patients at low or moderate CVR reclassified at high CVR were 6%,12%,14% and 32% after echocardiography,albuminuria,PWV and carotid ultrasound(CUS) respectively(X2 $p<0.001$ for all vs routine). Assessment of PWV in addition to echocardiography lead to an increase of the proportion of patients at high CVR (from 6% to 17%,$p<0.001$),as for PWV in addition to albuminuria (from 12 to 22%,$p<0.01$)but did not affect risk stratification in addition to CUS(from 32% to 35%, p ns).
Conclusion: Measurement of PWV may significantly change CVR stratification in addition to echocardiography and to detection of albuminuria, but not after CUS;our results confirm that evaluation of different forms of TOD is useful for a more accurate assessment of global CVR.

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P1.50
IS AORTIC PULSE WAVE VELOCITY A STRONGER MARKER OF CARDIOVASCULAR RISK THAN CALCULATED RISK SCORES IN YOUNGER WOMEN?

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Introduction: Younger women are considered to have low cardiovascular (CV) risk. Predictive scoring systems aim to assess overall CV risk from multiple risk factors to guide treatment decisions. Aortic pulse wave velocity (aPWV) may be a more efficient, 'integrated' CV index providing a more effective treatment target than risk factors alone. We examined the relationship of CV risk scores to aPWV in younger women.
Patients and Methods: 193 pre-menopausal women (age 36.2 years, 95% CI 35.1-37.2) underwent anthropometric, biochemical and aPWV measures. 10 year CV risk score was estimated using the Joint British Guidelines, similar to the Europe-wide 'Heartscore' initiative. BMI, waist & bio-impedance estimates of adiposity (fat mass index) were tested.
Results: CV risk scores were significantly higher in women who had had gestational diabetes (2.35%) than in those without (1.34%), $p=0.004$, but surprisingly were not for previous gestational hypertension (1.21 vs. 1.27 %). After adjusting for other CV risk modulators *not* included in risk scores, (social deprivation (Townsend's index), hsCRP, heart rate), residual independent influences on aPWV were:

	Beta	95% CI of beta	p
Fat mass index (kg/m2) (or BMI or Waist)	−0.09	-0.172 to -0.008	0.031
Calculated 10 year absolute CV risk	0.122	0.023 to 0.221	0.016

Conclusion: In young women, even without overt diabetes or hypertension, adjusting for other factors, current adiposity and calculated CV risk were independently related to aPVW. This suggests aPWV reflects the 'load' of CV risk at this age better than CV scores alone (which omit obesity indices).

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P1.51
EFFECTS OF ELECTRICAL BARORECEPTOR STIMULATION ON CENTRAL ARTERIAL HEMODYNAMICS ASSESSED IN A LARGE ANIMAL MODEL

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Electrical stimulation of the carotid baroreceptor has been shown to be an effective therapy for patients with (resistant) hypertension. However, the exact mechanism leading to blood pressure reduction is not fully elucidated. We measured left ventricular pressure and volume, ascending and abdominal aortic pressure using high-fidelity transducers in 9 anaesthetized dogs (24.8 ± 2.9 kg) at baseline and during electrical stimulation of the carotid baroreceptors. Therapy significantly (all $P<0.001$) lowered mean (from 81.1±7.6 to 54.8±5.5 mmHg), systolic (from 95.7±7.8 to 78.6±6.0 mmHg) and diastolic (from 66.6±8.3 to 41.4±6.2 mmHg) pressures. Cardiac output remained unchanged, but stroke volume tended to increase while heart rate decreased (83.5±15.3 to 67.2±19.3 beats/min, $P=0.002$). Systemic vascular resistance decreased from 1.25±0.50 to 0.92±0.44 AU, $P=0.002$). There was no change in central-to abdominal pulse transit time, and we could not unequivocally demonstrate a change in total arterial compliance. Therapy had a drastic effect on the morphology of the pressure waveforms and on the relationship between abdominal and central aortic pressure. Pressure was amplified at baseline but damping of the pressure pulse along the aorta was observed during stimulation, suggesting a drastic impact of therapy on pressure wave reflection. This was confirmed by a decrease in the magnitude of wave reflection (from 0.54±0.13 to 0.39±0.08, $P=0.014$). We conclude that, in an acute animal model, carotid baroreceptor stimulation significantly lowers blood pressure through vasodilation, with important effects on patterns of wave reflection. Further research is mandatory in experimental (conscious) models of hypertension and in patients.

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P1.52
REGULATION AND ACTIONS OF CARDIOTROPHIN-1 IN CULTURED RAT VASCULAR SMOOTH MUSCLE CELLS

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Cardiotrophin-1 (CT-1) is a cytokine belonging to the interleukin-6 superfamily that exhibits trophic and survival properties in a number of cell types. CT-1 expression has recently been identified within the media of atherosclerotic arteries, but its role in the vessel remains unknown. The aim of this study is to characterize CT-1 actions and regulation in vascular smooth muscle cells (VSMC). Primary rat aorta VSMC were stimulated with CT-1 (10^{-11}-10^{-9}M) for up to 48 hours, without and with antibodies against CT-1 receptors. Moreover, the effects of aldosterone (10^{-8}-10^{-6}M) and angiotensin II (10^{-9}-10^{-7}M) on CT-1 expression were evaluated. Cell proliferation was determined by MTT assay. The expression of CT-1, collagen type I, and fibronectin was quantified by Western blot. Matrix metalloproteinases (MMPs) activities were assessed by gelatin and casein zymographies. A 48-hour treatment with CT-1 induced VSMC proliferation in a dose-dependent manner ($p<0.01$). A 24-hour incubation with CT-1 led to an increased expression of collagen type I ($p<0.01$) and fibronectin ($p<0.05$), with a parallel and dose-dependent increase in active MMP-2 ($p<0.01$), MMP-3 ($p<0.05$) and MMP-9 ($p<0.01$), all of these effects being reversed in the presence of antibodies against CT-1 receptors. Whereas VSMC spontaneously expressed CT-1, both aldosterone and angiotensin II enhanced ($p<0.01$) CT-1 expression in these cells in a dose- and time-dependent manner. CT-1 induces proliferation and a secretory phenotype in VSMC. Upregulation of CT-1 expression by angiotensin II and aldosterone in VSMC suggests a mediator role for this cytokine in alterations of these cells caused by the RAAS in vascular diseases.

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P1.53
INTRINSIC VERSUS EXTRINSIC OXIDATIVE STRESS AND THEIR IMPACT ON ARTERIAL ELASTIC PROPERTIES: THE ROLE OF NADPH OXIDASE AND SMOKING ON WAVE REFLECTIONS AND AORTIC PRESSURES

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Purpose: The NADPH oxidase system produces superoxide (intrinsic oxidative load) while smoking is a well-established extrinsic oxidative factor. Carriers of the G allele (AG or GG) at position -930 of the CYBA gene of NADPH oxidase produce increased amounts of superoxide. We investigated the effect of intrinsic (NADPH produced) versus extrinsic (smoking) oxidative stress on arterial elastic properties.

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