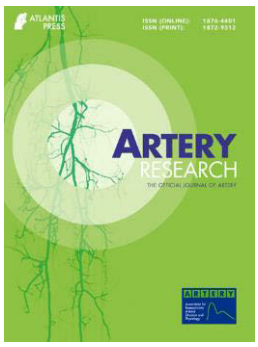

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09.01: EZETIMIBE AND SIMVASTATIN BOTH REDUCE INFLAMMATION, DISEASE ACTIVITY, AORTIC STIFFNESS AND IMPROVE ENDOTHELIAL FUNCTION IN RHEUMATOID ARTHRITIS

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stiffness remained significant [1.22 (1.02–1.47)] whereas estimates of pulse pressure were slightly decreased [1.13 (0.93–1.37)].
Conclusions: Aortic stiffness is an independent predictor of coronary heart disease in apparently healthy subjects.

04.04
AMBULATORY ARTERIAL STIFFNESS INDEX (AASI) PREDICTS STROKE IN A GENERAL POPULATION

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Background: The ambulatory arterial stiffness index (AASI), defined as one minus the regression slope of diastolic on systolic blood pressure in individual subjects, can be computed from 24-h ambulatory blood pressure recordings and predicted stroke in a large cohort of referred patients.
Methods: We investigated the prognostic value of AASI and 24-h pulse pressure (PP) in a sex- and age-stratified random sample of 1829 Danes, aged 40–70 years. We used Cox regression to adjust for sex, age, body mass index, mean arterial pressure, smoking, diabetes mellitus, and a history of cardiovascular disease. We also adjusted AASI for PP and vice versa.
Results: Over a median follow-up of 9.4 years, the incidence of fatal and nonfatal endpoints amounted to 40 for stroke, 150 for coronary heart disease, and 212 for cardiovascular events. In fully adjusted models, the relative hazard ratios associated with a 1 SD increase (0.14 units) in AASI were 1.61 (95% confidence interval, 1.14 to 2.27; $P = 0.007$) for stroke, 0.94 (0.78 to 1.12; $P = 0.46$) for coronary heart disease, and 1.04 (0.89 to 1.20; $P = 0.64$) for cardiovascular events. For PP, none of the fully adjusted ratios reached significance ($P > 0.45$). AASI still predicted stroke after excluding subjects with previous cardiovascular disease or after adjustment for systolic blood pressure instead of mean arterial pressure.
Conclusions: In middle-aged and older individuals randomly recruited from a European population, AASI was a strong predictor of stroke over and beyond traditional cardiovascular risk factors, including mean arterial pressure and PP.

07.01
REDUCING ARTERIAL STIFFNESS AND WAVE REFLECTION – QUEST FOR THE HOLY GRAIL?

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Arterial stiffness and wave reflection are fast emerging as therapeutic targets in their own right. While thiazide diuretics have little or no effect on either arterial stiffness or wave reflection, vasodilators including nitrates and phosphodiesterase type-5 inhibitors e.g., sildenafil, reduce wave reflections and aortic pressures but not aortic stiffness. ß-blockers have the opposite effect; they reduce aortic stiffness but increase aortic pulse pressure and wave reflections while calcium antagonists and α-blockers show varying effects on the vascular wall. Drugs targeting the renin–angiotensin–aldosterone system, namely angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) and aldosterone antagonists have been shown as the most effective in reducing both arterial stiffness and wave reflection, and in some cases, to a greater extent than predicted from the extent of blood pressure (BP) reduction. Also, there is evidence of an additive effect on arterial stiffness with combined ACEI and ARBs. Exploring further the synergistic effects of anti-hypertensive drugs on arterial stiffness, a polypill containing a low-dose combination of a thiazide diuretic, calcium antagonist, ß-blocker and an ACEI, decreased arterial stiffness more than the individual drugs in standard doses. However, beyond the dynamic effects of anti-hypertensive drugs, future therapies may directly target vascular structural alterations including collagen degradation, advanced glycation end-products, the matrix metalloproteinases and vascular inflammation. Finally, one can speculate about the role of pharmacogenomics which may help tailor *"de-stiffening therapy"* in individuals with stiff arteries.

07.02
INFLAMMATION AND ARTERIAL FUNCTION

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During the last decade, several studies have documented the unfavorable effects of inflammation on cardiovascular function and its role in the pathophysiology of atherosclerotic disease. The interplay between inflammation and arterial system is multifaceted. On the one hand, the arterial endothelium contributes to the initiation and the perpetuation of inflammation. On the other hand, the inflammatory cascade affects adversely the endothelium-dependent processes and the mechanical properties of the arteries. These effects give rise to impaired vasomotion, arterial stiffening and increased wave reflections and thus result in an unfavorable hemodynamic loading of the heart. Chronic inflammatory diseases (such as rheumatoid arthritis, and others) as well as acute inflammatory stimuli (such as acute infections) may adversely influence the arterial performance. Moreover, systemic subclinical low-grade inflammation, as expressed by high blood levels of inflammatory markers/mediators, is a common denominator of most cardiovascular risk factors (hypertension, diabetes, etc.) and importantly, it is closely related to impaired arterial elastic properties. In addition, vasculogenic erectile dysfunction, which comprises an alternative phenotype of arterial dysfunction and an emerging cardiovascular risk predictor, is accompanied by low-grade inflammatory activation. Among the several inflammatory markers/mediators, C-reactive protein level has been consistently associated with indices of arterial function in several populations. However, data regarding a possible direct etiological role of CRP in arterial dysfunction and atherosclerosis, if any, are yet inconclusive. Current evidence suggests that anti-inflammatory strategies benefit arterial function in several clinical settings. Further research is needed to elucidate whether inflammation may comprise a worthwhile treatment target regarding the cardiovascular system.

07.03
SODIUM EXCRETION AS A MODULATOR OF GENETIC INFLUENCE ON ARTERIAL STIFFNESS AND OTHER CARDIOVASCULAR PHENOTYPES

K. Stolarz[1]*, W. Wojciechowska[1], T. Kuznetsova[2,5], K. Kawecka-Jaszcz[1], S. Babeanu[3], E. Casiglia, J. Filipovský[4], J. Peleška, Y. Nikitin[5], J.A. Staessen[2]. *On behalf of the European Project On Genes in Hypertension (EPOGH) Investigators. [1]First Cardiac Department, Medical College, Jagiellonian University, Cracow, Poland, [2]Study Coordinating Centre, Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, University of Leuven, Leuven, Belgium, [3]San Luca Hospital, Bucharest, Romania, [4]Charles University, Pilsen, Czech Republic (J.F.); General Faculty Hospital, Prague, Czech Republic, [5]Institute of Internal Medicine, Novosibirsk, Russian Federation*

Hypertension is a chronic age-related disorder, affecting nearly 20% of all adult Europeans. This disease entails debilitating cardiovascular complications and is the leading cause for drug prescriptions in Europeans older than 50 years. Intensive research over the past two decades has so far failed to identify common genetic polymorphisms with a major impact on blood pressure or associated cardiovascular phenotypes, suggesting that multiple genes each with a minor impact, along with gene–gene and gene–environment interactions, play a role. The European Project on Genes in Hypertension (EPOGH) is a large-scale, family-based study in which participants from seven different populations were phenotyped and genotyped according to standardized procedures. The EPOGH demonstrated that phenotype–genotype relations strongly depend on host factors such as gender and lifestyle, in particular salt intake as reflected by the 24-h urinary excretion of sodium. Individuals with the same genetic predisposition had different vascular stiffness, left ventricular mass or heart rate variability, depending on whether they ate a high-sodium or a low-sodium diet. The EPOGH therefore highlights the concept that phenotype–genotype relations can only be studied within a defined ecogenetic context.

Free Communications (Young Investigators)

09.01
EZETIMIBE AND SIMVASTATIN BOTH REDUCE INFLAMMATION, DISEASE ACTIVITY, AORTIC STIFFNESS AND IMPROVE ENDOTHELIAL FUNCTION IN RHEUMATOID ARTHRITIS

K.M. Maki-Petaja*, A.D. Booth, F.C. Hall, S.M.L. Wallace, C.M. McEniery, A. Furlong, J. Cheriyan, J. Brown, I.B. Wilkinson. *University of Cambridge, Cambridge, United Kingdom*

Background and Aims: HMG-CoA reductase inhibitors (statins) have been shown to have anti-inflammatory and disease modifying properties in patients

with rheumatoid arthritis (RA). The aim of this study was to investigate the effect of simvastatin and ezetimibe on inflammation, disease activity, arterial stiffness and endothelial function in patients with RA and to test our hypothesis that cholesterol lowering per se can improve arterial stiffness and reduce inflammation.
Methods: 20 RA patients received simvastatin 20 mg and ezetimibe 10 mg in a double-blind cross over study. Blood pressure, aortic pulse wave velocity (PWV) and flow mediated dilatation response (FMD) were measured before and after each treatment. Serum inflammatory markers and disease activity were also determined. Data are mean changes±SEM, and significance was determined using 2-way repeated measures ANOVA.
Results: As expected both ezetimibe and simvastatin significantly reduce total cholesterol (-0.62±0.12 and -1.28±0.11 mmol/L, respectively; $P < 0.0001$). Both drugs significantly reduced CRP (-5.35±2.07 and -5.05±1.41 mg/L; $P = 0.0002$); disease activity (-0.74±0.24 and -0.50±0.18; $P < 0.0001$); aortic PWV (-0.69±0.26 and -0.71±0.16 m/s; $P = 0.0012$) and concomitantly, FMD was significantly improved (1.37±0.26 and 2.51±0.48%; $P = 0.0001$). Importantly, only the effect on total cholesterol differed significantly between the drugs ($P < 0.001$).
Conclusion: The present study shows, that both ezetimibe and simvastatin reduce inflammatory markers and disease activity to a similar extend in patients with RA. Moreover, aortic PWV was reduced with both drugs and concomitantly, endothelial function was improved. This suggests that cholesterol lowering per se has anti-inflammatory effects and improves vascular function.

09.02
RELATIONSHIP BETWEEN GROWTH AND AORTIC STIFFNESS IN EARLY YEARS OF LIFE

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Introduction: The exact course of aortic stiffness in early years of life is not known. This study was designed to test the relationship between aortic pulse wave velocity (aPWV) and the parameters of growth amongst children aged between 0 and 2 years. Our hypothesis was that aPWV is influenced by growth velocity.
Methods: Data was obtained from 517 baby-visits between 0 to 24 months of age, and included measurement of weight, length, blood pressure (BP) and aPWV.
Results: The weight, BMI and rate of BMI change are associated with aPWV and BP at birth, 1 and 2 years of age as shown in the table. aPWV

	Weight	At birth		1 year		2 years	
		Weight	BMI	BMI rate 0-1	Weight	BMI	BMI rate 0-2
aPWV	r = 0.29, p = 0.001						
SBP		r = 0.30, p < 0.001	r = 0.24, p = 0.002	r = 0.24, p = 0.006	r = 0.46, p < 0.001	r = 0.36, p < 0.001	r = 0.27, p = 0.013
DBP			r = 0.19, p = 0.017	r = 0.241, p = 0.007			

increased by 6% from birth to 12 months and 37% from 12 to 24 months with an overall increase from birth to 24 months of 45%. Adjusting for gender, ethnicity, weight-rate and height, pulse pressure was found to be independently influenced by pulse pressure at age of 1 year (Beta = -0.027, p = 0.030; 95% CI -0.05 to -0.003), but this association was lost at age of 2 years.
Conclusions: Aortic stiffness is associated with increasing age, weight and BMI, as well as the rate of change of the latter two. All these variables are recognised cardiovascular risk factors and should be controlled from an early age.

09.03
MULTI-AXIAL MECHANICAL CHARACTERISTICS OF CAROTID PLAQUE IN HYPERTENSIVES ASSESSED BY MULTI-ARRAY ECHOTRACKING SYSTEM

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The vulnerability to rupture of carotid plaque depends on the various types of mechanical stress including higher circumferential wall stress (CWS) in hypertensives and histological characteristics of plaque.
Objective: determine the multiaxial mechanical deformations of the common carotid artery (CCA) with an echotracking system allowing measurement of thickness, diameter, strain, distensibility, elastic modulus (Einc) and CWS on 4 cm long CCA segments including plaque. This allowed us to determine a longitudinal bending stress (BS) equal to the ratio of strain at the level of plaque to strain of adjacent CCA.
Patients: we included 25 patients with a recent cerebrovascular ischemic event and a plaque on CCA homolateral to stroke territory. We divided patients into two groups according to BS behaviour: pattern A (outward BS, larger strain at plaque site than on CCA), pattern B (inward BS).
Results: 16 patients belonged to pattern A and 8 patients to pattern B. Prevalence of dysplipidemia and diabetic were higher in pattern B (100% *vs* 56%, $p = 0.03$ and 63% *vs* 12%, $p = 0.04$). In pattern B distensibility was significantly lower at the level of plaque than in CCA it was the converse in A patients (13.1±6.5 *vs* 18.2±3.9, $p < 0.003$ and 22.3±11.2 *vs* 16.6±12.4 $kPa^{-1}10^{-3}$, $p < 0.001$). Pattern A patients had lower Einc at the level of the plaque than of CCA (374±173 *vs* 802±669 kPa, $p < 0.01$) the opposite was observed in B patients (739±497 *vs* 543±146 kPa, $p < 0.01$). CWS in CCA was higher in B than in A patients (83±16 *vs* 65±15 kPa, $p < 0.01$), plaque CWS was similar in the two groups (60±7 vs 53±13 kPa, NS).
Conclusion: type 2 diabetes and dyslipidemia were associated with a stiffer plaque than adjacent CCA. These results suggest that the higher risk of plaque complication, reported in patients with diabetes and hypercholesterolemia, may be due to a specific pattern of strain gradient between plaque and adjacent CCA.

09.04
A UNIFYING EXPLANATION OF THE AORTIC PULSE WAVEFORM IN HUMANS

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Introduction: Despite more than 200 years of research, no model has been able to fit all the aortic pressure waveform with physiologically interpretable parameters. We propose that the arterial waveform is composed of two components: (1) an arterial windkessel which stores ejected blood during systole and discharges it during diastole and (2) waves originating from the left ventricle and distal reflection sites.
Method: In 19 subjects (age 54±13 years) we measured simultaneous pressure and velocity in the aorta. The windkessel component of the pressure wave was calculated, and forward and backward waves were identified as previously described [1]. The peak contribution of each component was calculated after subtraction of the diastolic pressure.
Result: In the human aorta, the initial rise in pressure was due to a wave arising from the left ventricle (Figure 1). This wave was responsible for 20 mmHg (29%) of the total rise in pressure. Windkessel pressure was responsible for 40 mmHg (57%) of the total pressure rise. Reflected waves were responsible for 10 mmHg (14%) of the total rise in pressure.

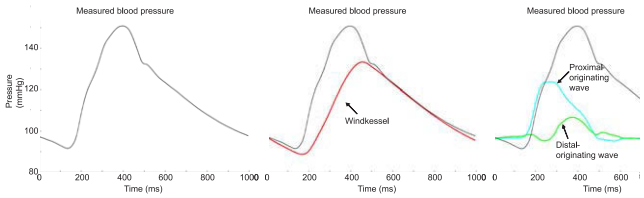

Fig. 1.

Conclusions: Using this new approach we have shown that the aortic pressure wave consists of three principal components. The systolic rise in pressure in the aorta is largely determined by a windkessel and waves arising from the left ventricle. Reflected waves make only a minor contribution. Waves do not contribute to the pressure and flow in diastole. Diastolic pressure is due to capacitative discharge of pressure from the Windkessel.

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