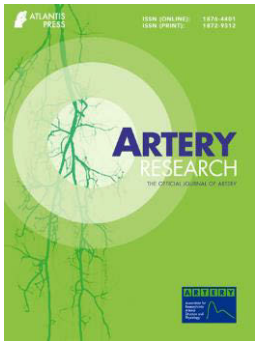

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# 06.02: RELATION OF AORTIC STIFFNESS WITH ECHOCARDIOGRAPHIC INDICES OF LEFT VENTRICULAR DIASTOLIC FILLING AND LONGITUDINAL VELOCITIES IN SUBJECTS FREE OF CLINICAL CARDIOVASCULAR DISEASE

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differences for AIx were not observed (change -0.62% and +0.44%, p=0.48). As expected, a significant reduction in CRP (-9.2 mg/l, p=0.011) and DAS28 for the RA patients (-0.73, p=0.002) was observed in the treatment group, but we did not find significant correlations between change in aPWV and CRP in the entire treatment group (r=0.055, p=0.785) and between change in aPWV and DAS28 in the RA group (r=0.091, p=0.737).
**Conclusion:** These findings indicate that anti-TNF-alpha therapy ameliorates functional parameters of early atherosclerosis. However, changes in aPWV were not correlated to improvement in markers of inflammatory activity.

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### 04.03
### LIFE-COURSE HABITUAL PHYSICAL ACTIVITY AND ITS IMPACT ON ARTERIAL STIFFNESS: THE AMSTERDAM GROWTH AND HEALTH LONGITUDINAL STUDY (AGAHLS)

R.J.J. van de Laar [1], I. Ferreira [1], M.H. Prins [1], J.W.R. Twisk [2], C.D.A. Stehouwer [1].
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**Purpose:** To examine how the development over time (i.e. from adolescence to adulthood) of habitual physical activity (HPA) impacts on arterial stiffness (AS) of both the elastic carotid (CCA) and the muscular femoral (CFA) arteries in adulthood.
**Methods:** Longitudinal data on HPA (expressed in metabolic equivalents/week − METs/wk) were retrieved from the AGAHLS (*n=373*, 196 women, 8 follow-up measures between the ages of 13 and 36 yrs). AS (i.e. CCA and CFA distensibility and compliance coefficients and CCA's Young's elastic modulus) was assessed by non-invasive ultrasonography when subjects were 36 yrs old; a sex-specific AS score for each artery was calculated by averaging the height and MAP-adjusted z-scores of each of these estimates. Generalized estimating equations were used to compare the mean levels of HPA throughout the 24-yr follow-up period between those subjects with 'stiffer' (i.e. lowest quartile) *vs.* 'normal' (highest 3 quartiles of AS score) arteries at the age of 36.
**Results:** Compared to subjects with 'normal', those with 'stiffer' CCA and CFA arteries had spent, on average and throughout the longitudinal period, 376 and 500 less METs/week on HPA (corresponding to @ 9 to 12 min/day of light-to-moderate intensity bicycling), respectively (Table). Adjustments for other risk factors (RFs), in particular cardiopulmonary fitness, explained these differences to a large extent for the CCA, but other RFs may also explain the association between HPA and CFA stiffness.

**Conclusion:** Promoting increases in HPA during adolescence and throughout the course of life may prevent the development of AS, partially due to its beneficial effects on fitness and other cardiovascular RFs.

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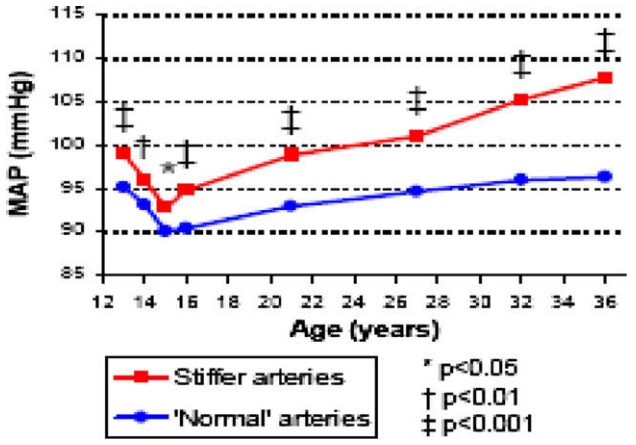
### 06.01
### LIFE-COURSE OF MEAN ARTERIAL PRESSURE AND ITS IMPACT ON ARTERIAL STIFFNESS: THE AMSTERDAM GROWTH AND HEALTH LONGITUDINAL STUDY (AGAHLS)

I. Ferreira [1], R.J.J. van de Laar [1], M.H. Prins [1], J.W.R. Twisk [2], C.D.A. Stehouwer [1].

| Model: adjustments | Stiff vs. normal CCA | | Stiff vs. normal CFA | |
|---|---|---|---|---|
| | β | 95% CI | β | 95% CI |
| 1. time, sex, height, smoking, alcohol, energy intake | −376 | −724; −27 | −500 | −839; −161 |
| 2. + body fatness (sum of 4 skinfolds) | −317 | −668; 34 | −471 | −810; −132 |
| 3. + cardiopulmonary fitness ($VO_2$max) | −172 | −510; 166 | −386 | −712; −60 |
| 4. + blood lipids (total−to−HDL cholesterol ratio) | −234 | −585; 117 | −489 | −826; −152 |
| 5. + resting heart rate | −328 | −670; 15 | −461 | −794; −128 |
| 6. + systolic blood pressure | −350 | −709; 8 | −482 | −828; −136 |
| 7. + all variables in models 2 to 6 | −145 | −490; 201 | −422 | −750; −93 |

[1] *University Hospital Maastricht, Maastricht, Netherlands*
[2] *VU University Medical Center, Amsterdam, Netherlands*

**Purpose:** To investigate how the development over time (i.e. from adolescence to adulthood) of mean arterial pressure (MAP) impacts on arterial stiffness in adulthood.
**Methods:** Longitudinal data on systolic (SP) and diastolic (DP) blood pressure were retrieved from the AGAHLS (*n=373*, 196 women; 8 follow-up measures between the ages of 13 and 36 yrs). MAP was calculated as [(2*DP)+SP]/3. Arterial stiffness (i.e. carotid, brachial and femoral distensibility and compliance coefficients) was assessed by non-invasive ultrasonography when subjects were 36 yrs old; a sex-specific total stiffness score was calculated by averaging the height and local MAP-adjusted z-scores of each of these estimates. Generalized estimating equations were used to compare the mean levels (and the patterns of development) of MAP throughout the 24-yr follow-up period between subjects with 'stiffer' (i.e. lowest quartile) *vs.* 'normal' arteries (highest 3 quartiles of the total stiffness score) at the age of 36.
**Results:** Compared to subjects with 'normal', those with 'stiffer' arteries had, on average, 6.36 mmHg (95%CI: 5.04; 7.67) greater levels of MAP throughout the longitudinal period. These differences were already present in adolescence and were further amplified thereafter with subjects with stiffer arteries showing a steeper increase in MAP between adolescence and age 36 (Figure). Adjustments for other risk factors (i.e. smoking behaviour, energy and alcohol intake, physical activity, body fatness, blood lipids and heart rate) only slightly attenuated these differences.




**Conclusion:** Blood pressure monitoring should start already in early age in order to avoid/delay arterial stiffening and related cardiovascular complications.

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### 06.02
### RELATION OF AORTIC STIFFNESS WITH ECHOCARDIOGRAPHIC INDICES OF LEFT VENTRICULAR DIASTOLIC FILLING AND LONGITUDINAL VELOCITIES IN SUBJECTS FREE OF CLINICAL CARDIOVASCULAR DISEASE

E. Malshi [1], C. Morizzo [1], M. Kozàkovà [1], A.G. Fraser [2], C. Palombo [1].
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**Introduction:** a relation between aortic stiffening (AS) and LV systolic dysfunction and hypertrophy is established in the elderly. A relation between AS and LV diastolic function can be hypothesized, mediated by age and increased LV mass (LVM).
**Aim:** to verify whether AS may affect LV diastolic function independently of LVM and age in subjects with preserved systolic function.
**Methods:** 144 subjects below 65 years, (59 controls: age 40±12, MBP 84±7 mmHg; and 85 patients with at least one major risk factor, free of CV disease, age 42±16, mean BP 96±12 mmHg). LV mass, systolic function, diastolic filling

were assessed by Echo-Doppler. Early and late diastolic mitral annulus longitudinal velocities (E' and A') were assessed by tissue velocity imaging. AS was estimated by carotid-femoral pulse wave velocity (PWV).
**Results:** compared to controls, patients had higher ($p<0.05$-0.001) PWV (9.4±2 vs 8.0±1 m/s) and lower transmitral E/A ratio (1.2±0.5 vs 1.4±0.4, $p<0.01$); no significant differences were found for LV midwall shortening (116±13 and 119±13%), and EF (67±6 and 69±5%). In the overall population, transmitral E/A correlated inversely ($p< 0.01$) with age ($r=-0.60$), SBP ($r=-0.37$), DBP ($r=-0.50$), LVMI ($r=-0.43$), and PWV ($r=-0.51$). In multivariate analysis, PWV remained independent predictor of E/A, together with age, SBP and DBP (adjusted $R^2$ 0.43, $p < 0.05$). E'/A' showed a similar correlation pattern as E/A.
**Conclusion:** in subjects free of CV disease and with preserved LV systolic function, AS affects LV diastolic filling and longitudinal myocardial velocities independently of age, LVM and BP.

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### 06.03
### COLLAGEN ACCUMULATION IS A SIGNIFICANT CONTRIBUTOR TO PULMONARY HYPERTENSION-INDUCED LARGE ARTERY STIFFENING

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*University of Wisconsin, Madison, WI, USA*

Hypoxic pulmonary hypertension (HPH) leads to large pulmonary artery (PA) stiffening, which affects right ventricular afterload. We hypothesized that vascular collagen accumulation is the major cause of large PA stiffening in HPH. The hypothesis was tested with transgenic mice that synthesize collagen type I resistant to collagenase degradation ($Col1a1^{R/R}$) and wild-type controls. Animals were exposed to hypoxia for 10 days and then allowed to recover. Main PAs were harvested for mechanical and biochemical tests. Effects of smooth muscle cells (SMCs) were examined using the vasoactive agents U46619 and Y27632. Pressure-diameter testing showed that left PAs of both $Col1a1^{R/R}$ and wild-type mice stiffened with hypoxia ($p<0.01$). Measurement of hydroxyproline biochemically confirmed that PA collagen content increased as well ($p<0.01$). After recovery, wild-type PAs were less stiff ($p<0.01$), whereas $Col1a1^{R/R}$ PAs remained stiffened; biochemically, collagen content tended to decrease in both strains although less so in the $Col1a1^{R/R}$. Interestingly, after hypoxia, $Col1a1^{R/R}$ PAs were less stiffened than those of wild-type mice. We speculate that differences in mean PA pressure during the 10 days of hypoxia between strains are responsible. Consistent with our hypothesis, $Col1a1^{R/R}$ PAs also accumulated less collagen in response to hypoxia than wild-type mice. In the recovery group, stiffness and collagen content were comparable between strains. Quantitation for elastin showed no significant differences between groups. No significant differences between exposures and strains were observed in the mechanical effects of SMCs. The correlation between mechanical and biological properties suggests that collagen accumulation is critical to HPH-induced PA stiffening.

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### 06.04
### THE COMBINED EFFECT OF HIGH PULSE WAVE VELOCITY AND AUGMENTATION INDEX PREDICTS MORTALITY IN AN ELDERLY POPULATION: THE PROTEGER STUDY

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**Objective:** Carotid — femoral aortic stiffness (PWV) and pressure wave reflections (AI), both markers of cardiovascular mortality, are considered to increase in parallel. A disassociation between PWV and AI has been described. In a cohort (PROTEGER study) of old population (85.4±0.5) has been previously observed that neither PWV nor AI, were predictors of mortality. The aim of the present analysis was to investigate the association between PWV and AI as well as their combined effect on mortality.
**Methods:** Pulse wave analysis was applied in 259 subjects for the assessment of PWV and AI. The population was divided and analyzed according to tertiles of PWV and AI.
**Results:** Eighty-seven subjects died during the follow up (2 years). No association was found between PWV and AI. The subjects with combined high PWV (3rd tertile) and high AI (2nd and 3rd tertiles) [group a] had significantly higher mortality compared to the rest of the population [group b] (27/56: 48.6% vs 61/203: 30.1%, $p<0.05$, Kaplan Mayer log-rank $p=0.003$). No significant differences were found between group a and b regarding cardiovascular (CV) risk factors. Cox regression analysis showed that group a had higher mortality independently from age, gender, cardiovascular (CV) history and classical CV risk factors.
**Conclusion:** PWV and AI were not independent predictors of mortality. However, those subjects with combined increase of PWV and AI have higher mortality suggesting that: (i) the effect of PWV is more prominent in the presence of increased AI and (ii) that the disassociation between PWV and AI may be related to reduced mortality.

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### 06.05
### PULSE WAVEFORM CHARACTERISTICS OR CENTRAL PRESSURE INDICES TO PREDICT ADVERSE CARDIOVASCULAR OUTCOMES IN CORONARY PATIENTS

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**Background:** Pulse waveform characteristics (Augmentation Index — AIx, Pressure Augmentation — AP, Pulse wave transit time — Tr) as well as central pressure indices (aortic pulse pressure — aoPP, pulse pressure amplification — PPAmp, pulsatility — aortic PP/mean blood pressure) have been shown to predict cardiovascular events. We aimed to determine their relative predictive value.
**Methods:** We prospectively assessed AIx, AIx@75, AP, Tr as well as aoPP, PPAmp and pulsatility, using radial applanation tonometry and a validated transfer function, in 520 male patients undergoing coronary angiography. Primary endpoint was a composite of all cause mortality, myocardial infarction, stroke, cardiac, cerebrovascular and peripheral revascularization. Statistics used were Cox proportional hazards regression models.
**Results:** Mean age was 63 years, 66.7% were hypertensives, 79.2% had CAD. During a follow up of 49.4 months, 170 patients reached the primary endpoint.
All pressure waveform characteristics and central pressure indices predicted the primary endpoint: When divided into tertiles according to the various indices, patients in the first tertile had an unadjusted HR for the combined endpoint of 0.477 (0.328-0.727) for AIx, 0.492 (0.339-0.744) for AIx@75, 0.468 (0.314-0.698) for AP, 0.435 (0.302-0.647) for Tr, 0.468 (0.331-0.685) for aoPP, 0.586 (0.406-0.858) for PPAmp, and 0.585 (0.407-0.839) for pulsatility, when compared to patients in the third tertile. However, after adjustment for age, extent of coronary disease, and brachial blood pressures, only AIx, AIx@75, and Tr remained significant predictors of the combined endpoint.
**Conclusion:** In male patients undergoing coronary angiography, pulse waveform characteristics, but not central pressure indices, consistently and independently predict cardiovascular events.

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### 06.06
### EVIDENCE OF AUGMENTATION OF SYSTOLIC CORONARY BLOOD FLOW BY RETROGRADE WAVE REFLECTION TRAVELLING-BACK FROM THE PROXIMAL AORTA

J.E. Davies [1], Z.I. Whinnett [1], N. Hadjiloizou [1], J. Aguado-Sierra [1], K. Parker [2], D.P. Francis [1], A.D. Hughes [1], J. Mayet [1].
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**Background:** It has been proposed that blood flow in coronary arteries is augmented by waves travelling-back from the distal aorta. However, these waves have never been identified. We used wave intensity analysis to time and quantify reflected waves travelling from the proximal aorta into coronary arteries, and assess their contribution to changes in coronary blood flow with ageing and hypertension.
**Method and Results:** In 19 subjects (age 35-73 years) sensor-tipped intra-arterial wires were used to measure pressure and Doppler velocity in the coronary arteries and at proximal aortic root. Separated wave intensity analysis was used to identify and quantify incident and reflected waves. The reflected wave in the proximal aorta occurred in systole in all subjects (159±12ms after the ECG-R-wave) and could be seen later in the coronary arteries: left main stem (186.8±10.7 ms), circumflex (188.8±7.4 ms) and left anterior descending (194.4±7.7 ms). In the coronary arteries the mean reflected wave represented 20.3±2.1% of the incident wave magnitude, and elicited a 38.9±8.4% instantaneous increase in systolic coronary blood flow velocity (0.2 to 0.28m/s, $p<0.002$). This augmentation was seen to increase with increasing age ($r=0.51$, $p<0.03$), probably