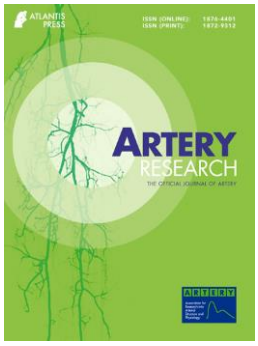

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4.4: FORWARD AND BACKWARD WAVES AT THE AORTIC ROOT: STEADY-STATE AND WAVE RE-REFLECTION CONSIDERATIONS

Timothy Phan*, John Li, Vandan Panchal, Amer Syed, Ejaz Shah, Julio Chirinos

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P = 0.035). By contrast, cAIx, as well as none of central and peripheral BP-derived parameters were significantly associated with cerebral lesion growth in univariate analysis. In multivariable regression logistic model, CF-PWV predicted cerebral lesion growth with an odds ratio of 1.43 [1.00—2.04], independently of age, and peripheral pulse pressure.
Conclusions: Increased aortic stiffness is independently associated with cerebral lesion growth in patients with acute ischemic stroke. Its deleterious effect is more important than that of BP.

4.1
EFFECT OF ALISKIREN ON VASCULAR REMODELING IN SMALL RETINAL CIRCULATION

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Background: In hypertension changes in small arterial structure are characterized by an increased wall-to-lumen ratio (WLR). These adaptive processes are modulated by the renin angiotensin system. It is unclear whether direct renin inhibitors exert protective effects on small arteries in hypertensive patients.
Methods: In this double-blind, randomized, placebo-controlled study (www.clinicaltrials.gov: NCT01318395) 114 patients with primary hypertension were after 4 weeks of standardized open-label treatment with valsartan 320 mg (run-in phase) randomized to additional therapy with either placebo or aliskiren 300 mg for 8 weeks. Parameter of arteriolar remodeling was WLR of retinal arterioles (80—140 μm) assessed non-invasively and in vivo by scanning laser Doppler flowmetry (Heidelberg Engineering, Germany). In addition, pulse wave analysis (SphygmoCor™, AtCor Medical, Australia) and pulse pressure (PP) amplification were determined.
Results: In the whole study population no clear effect of additional therapy with aliskiren on vascular parameters was documented. When analyses were restricted to patients with vascular remodeling, defined by median of WLR > 0.3326 (n = 57), WLR was reduced after 8 weeks by the treatment with aliskiren compared to placebo (−0.044 ± 0.07 versus 0.0043 ± 0.07, p = 0.015). Consistently, after 8 weeks of on-top treatment with aliskiren there was an improvement of PP amplification compared to placebo (0.025 ± 0.07 versus −0.034 ± 0.08, p = 0.013), indicative of less stiff arteries in the peripheral circulation.
Conclusion: Thus, our data indicate that treatment with aliskiren, given on top of valsartan therapy, improves altered vascular remodeling in hypertensive patients.

4.2
THE INHOMOGENEITY OF DIASTOLIC-SYSTOLIC RISE TIME OF THE DISTENSION WAVEFORM DISTRIBUTION IN THE COMMON CAROTID ARTERY IS ASSOCIATED WITH LIPID PRESENCE OF DISTAL PLAQUES

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Objectives: Diastolic-systolic rise time characteristics of the distension waveform distribution, i.e., mean and inhomogeneity, might be modified by wave reflections from distal plaques. The aim of this study is to investigate the association between rise time characteristics for the common carotid artery (CCA) and composition of distal plaques.
Methods: Longitudinal B-mode ultrasound (US) registrations of the CCA of 129 patients (age 69 ± 9) were performed with a Philips IU22 scanner. All patients had a plaque in the ipsilateral bifurcation and recently experienced a cerebrovascular accident. Distension waveforms were extracted by edge tracking and the diastolic-systolic rise time and its inhomogeneity, defined as standard deviation of systolic-diastolic rise time distribution for an artery segment, were derived. Plaque composition was extracted from 3T-MRI measurements (N = 125).
Results: 118 subjects had both an adequate MRI and US registration. 58% of the plaques had a lipid-rich necrotic core (LRNC) of which 68% had a thin fibrous cap (FC). Lipids were demonstrated in the proximal part in 51 plaques (43%). Mean CCA diastolic-systolic rise time (162 ± 26 ms) did not vary with plaque composition (Student t-test, p-value > 0.2). The inhomogeneity, however, was significantly lower for vulnerable distal plaques (mean difference LRNC: 8ms, FC: 11ms, Student t-test, p-value < 0.02) and, more specifically, when lipids were present in the proximal part of the plaque (mean difference 12ms, Student t-test, p-value < 0.001).
Conclusion: Diastolic-systolic rise time inhomogeneity of CCA distension is associated with the lipid presence of distal plaques.
This research was supported by the Center for Translational Molecular Medicine and the Dutch Heart Foundation.

4.3
THE EFFECT OF GLYCAEMIC STATE TRANSITION ON ACCELERATED AORTIC STIFFENING: A LONGITUDINAL STUDY IN THE WHITEHALL II COHORT

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In 4,759 participants from the Whitehall II study, we examined the impact of glycaemic history on aortic stiffening. Assessment of aortic stiffness by carotid-femoral pulse wave velocity (PWV) was performed twice with a 4 year interval (2007—2009 and 2012—2013). At the first aortic stiffness assessment and 5 years earlier (2002—2004 and 2007—2009 respectively), participants were categorised into 3 groups based on measurements of fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), and HbA_{1c}: normoglycaemia, dysglycaemia and type 2 diabetes. The impact of 5-year glycaemic state transition on PWV and PWV changes was analysed by mixed effect models adjusting for relevant confounders. In participants who had normoglycaemia on FPG, 2hPG and HbA_{1c} on both examinations, PWV was 8.3 m/s at baseline and increased by 0.4 m/s during 4 years. Those who progressed to dysglycaemia had a 0.3 m/s (95% CI: 0.1;0.5) steeper increase in PWV compared with stable normoglycaemia, whereas those who progressed to diabetes did not have a statistical significantly steeper increase in PWV (0.1 m/s (95% CI: −0.4; 0.6)). Participants with diabetes at both examinations had a markedly larger increase in PWV of 0.6 m/s (95% CI: 0.3;0.9) compared to participants with stable normoglycaemia. For other glycaemic state combinations there was a tendency towards a steeper increase in PWV compared with stable normoglycaemia, however not statistically significant. These results indicate that people with diabetes or deteriorating dysglycaemia, experience accelerated aortic stiffening; suggesting that prevention of dysglycaemic progression and diabetes may have a beneficial effect on the progression of aortic stiffness.

4.4
FORWARD AND BACKWARD WAVES AT THE AORTIC ROOT: STEADY-STATE AND WAVE RE-REFLECTION CONSIDERATIONS

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Background: The assumption of steady-state oscillation is often overlooked when arterial pressure and flow waveforms are decomposed into backward (P_b) and forward waves (P_f). This has led to various misinterpretations including a significant reflection-free time during early-systole and attribution of the P_f to solely a product of left ventricular contraction and proximal aortic properties.

Methods: Aortic pressure and flow were measured in anesthetized, open-chest dogs (n = 5). Wave reflections were modified with i.v. infusion of methoxamine (MTX) to increase reflections and nitroprusside (NTP) to decrease reflections. In a human sample (n = 226), central pressure and flow were measured using carotid tonometry and phase-contrast MRI, respectively.
Results: Under conditions of baseline and increased reflections in both dogs and humans, peak of the forward wave (FWA) consistently occurred after time of peak flow ($P < 0.001$). FWA was systematically greater than peak flow multiplied by aortic characteristic impedance ($Q_{max}Z_c$) in dogs ($P < 0.01$) and humans ($P < 0.01$). Only when wave reflections were abolished vasoactively (NTP) in dogs was time of FWA and peak flow the same, leading to insignificant differences in FWA and $Q_{max}Z_c$ ($P = 0.59$).
Conclusion: In steady-state, wave reflections set up in previous cardiac cycles, wave re-reflections at the aortic root, and proximal reflections contribute to both the P_f and P_b waves, even during early-systole. Most importantly, peak aortic flow is also determined by aortic input impedance, which includes effects from properties distal of the proximal aorta. Under steady-state conditions, forward wave amplitude and morphology cannot be attributed solely to the LV and proximal aorta.

4.5
A SYSTEMATIC REVIEW AND META-ANALYSIS OF CENTRAL TO BRACHIAL BLOOD PRESSURE AMPLIFICATION IN PATIENTS TYPE 2 DIABETES MELLITUS

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Background: Brachial blood pressure (BP) may not reflect central BP due to systolic BP (SBP) amplification. Patients with type 2 diabetes mellitus (T2DM) elicit vascular irregularities that may affect SBP amplification or other central BP indices (including pulse pressure [PP], augmentation pressure [AP] and augmentation index [AIx]). By systematic review and meta-analysis, this study aimed to determine the magnitude and variation of central-to-brachial SBP and PP amplification, AIx and AP in T2DM compared to non-diabetic controls.
Methods: Online databases were searched for published studies reporting invasive or non-invasive central and brachial SBP in T2DM and non-diabetic controls. Random effects meta-analyses and meta-regression were used to analyse the studies.
Results: We identified 17 studies with a total of 2,711 T2DM and 10,460 non-diabetic controls. There was no significant difference in SBP amplification between groups (T2DM = 10.8, non-diabetic = 10.2 mmHg; pooled estimate = 0.6 mmHg, 95%CI −0.3, 1.5, $p = 0.21$), but large variation in both (T2DM range = 2.0—16.6 mmHg, non-diabetic range = 1.0-16.1 mmHg). In the meta-regression, duration of T2DM explained 16.3% of the variance in the pooled data ($p = 0.15$); the difference in amplification between groups increasing by 0.3 mmHg per year of T2DM. PP amplification was not significantly different between groups ($p = 0.16$). AP, AIx and AIx corrected for heart rate were significantly higher in T2DM ($p < 0.05$ all).
Conclusions: Patients with T2DM have increased AP and AIx, but no difference in SBP (or PP) amplification compared to non-diabetic individuals. However, SBP amplification is highly variable and increases with duration of T2DM; altogether confirming that central systolic loading cannot be reliably estimated from brachial BP in T2DM.

4.6
RELATIONSHIP OF CAROTID ARTERIAL FUNCTIONAL AND STRUCTURAL CHANGES TO LEFT ATRIAL VOLUME INUNTREATED HYPERTENSION

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The contribution of arterial functional and structural changes to left ventricular (LV) diastolic dysfunction has been the area of latest research. There are some studies on the relationship of arterial stiffness (a.s.) and left atrial (LA) remodeling as a marker of diastolic burden. Little is known on the association of arterial structural changes and LA remodeling in hypertension (H).
The aim of this study was to examine the relationship of carotid a.s. and intimamedia thickness (IMT) to LA volume in subjects with H.
The study included 245 previously untreated hypertensives (166 women and 79 men, mean age 53.7 ± 11.8 years). Each patient was subjected to echocardiography with measurement of LA volume, evaluation of left ventricular hypertrophy (LVH) and LV systolic/diastolic function indices, integrated assessment of carotid IMT and echotracking of a.s. and wave reflection parameters.
Results: The following parameters were identified as independent determinants of indexed LA volume on multivariate regression analysis: diastolic blood pressure (beta = −0.229, $p < 0.001$), left ventricular mass index (LVMI; beta = 0.258, $p < 0.001$), E/e' index (ratio of early mitral flow wave velocity - E to early diastolic mitral annular velocity-e'; beta = 0.266, $p = 0.001$), augmentation index (AI; beta = 0.143, $p = 0.008$) and bodymass index (BMI; beta = 0.132, $p = 0.017$). No correlations between indexed LA volume and IMT were found.
Conclusion: There is a significant relationship of carotid arterial stiffness but not intima-media thickness to LA volume in patients with untreated hypertension.

5.1
INERTIAL-VISCOELASTIC MINIMAL MODEL OF THE ARTERIAL SYSTEM RECONCILES ARTERIAL COMPLIANCE ESTIMATIONS

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Background: The arterial system is viscoelastic rather than purely elastic. There exist various methods to characterize the purely elastic nature of arterial compliance, each method yielding different values. The pulse pressure method (C_{PPM}), estimating compliance by matching the pulse pressure (PP) of a two-element Windkessel to measured PP, yields consistently lower values than the pressure decay time method (C_{dec}) and diastolic area method (C_{area}). An alternative inertial-viscoelastic model (IVEMM) that is viscoelastic and frequency-dependent rather than purely elastic and constant has been shown in dogs to reconcile the various compliance estimation methods. We assessed the presumed merits of IVEMM compliance estimates in a clinically diverse human sample.
Methods: Central pressure and flow were measured using carotid tonometry and phase-contrast MRI, respectively, in 226 subjects. Arterial compliance was estimated using (1) C_{ppm}; (2) C_{dec}; (3) C_{area}; (4) $C_{IVEMM}(j\omega)$.
Results: C_{ppm} was nearly perfectly correlated with C_{IVEMM} evaluated at frequency of heart rate (Pearson coefficient (ρ) = 0.99; slope (B) = 1.00; $P < 0.001$). C_{area} ($\rho = 0.979$; $B = 0.928$; $P < 0.001$) and C_{dec} ($\rho = 0.974$; $B = 0.954$; $P < 0.001$) were very strongly correlated with C_{IVEMM} evaluated at 0 hertz (static compliance).
Conclusion: C_{PPM} is fit to PP defined in systole, when fast-acting phenomena are likely to elicit viscoelasticity of the arterial system. Its consistently lower values compared to C_{dec} and C_{area} are clarified by IVEMM to be the result of estimating viscoelastic compliance at frequency of heart rate. C_{dec} and C_{area} are estimates of static compliance. Consistent with dog studies, IVEMM appears to reconcile the three popular compliance estimation techniques.

5.2
SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS AND AORTIC STIFFNESS IN GENERAL POPULATION

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It has been suggested that accumulation of advanced glycation end-products (AGE) is involved in several pathophysiological processes in the vessel wall. Soluble isoform of receptor for AGE (sRAGE) acts as a decoy for capturing circulating AGE, prevents them from binding to the cell-surface receptor and protects against the RAGE-AGE axis-elicited processes. We hypothesized that low sRAGE levels might be associated with increased arterial stiffness.