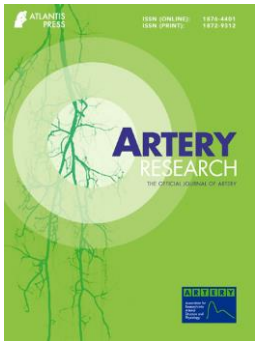

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3.4: WAVE INTENSITY ANALYSIS PROVIDES NOVEL INSIGHTS INTO PULMONARY HYPERTENSION

Junjing Su, Charlotte Manisty, Kim H. Parker, Soren Mellemkjaer, Luke Howard, Ulf Simonsen, Alun Hughes

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3.1
REDUCING ARTERIAL STIFFNESS INDEPENDENTLY OF BP: PROOF OF CONCEPT? CAVI, PWV AND CARDIAC DATA IN THE 6-MONTH VASERA TRIAL

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Purpose/ background/ objectives: People with or at risk of Type II diabetes (T2DM) are at increased risk of vascular disease and arterial stiffness (AS). We hypothesized that spironolactone and dietary nitrate (beetroot juice) separately and together would reduce AS, measured as cardiac-ankle vascular index (CAVI Fukuda Denshi, Japan mainly BP-independent) or aortic pulse wave velocity (PWV).
Methods: 126 (60% T2DM) were randomized, double-blind to spironolactone ($\leq$50mg) or doxazosin (control $\leq$16mg) and active/ placebo juice ($\leq$9/ 0mmol) daily. AS and echocardiographic measures (on a subgroup) were performed. Intention-to-treat analysis adjusted for between-group blood pressure (BP) change over time was performed using SAS.
Results: Change in (Δ)BP was not different between spironolactone and doxazosin (mean -6.7mmHg), nor between the juices. ΔCAVI was marginally reduced on doxazosin compared to spironolactone (-0.11[-0.30,0.08] vs. 0.14[-0.06,0.34] units, $p=0.080$) but more for aortic PWV (-0.44 [-0.69,-0.20] vs. -0.07 [-0.32,0.18]ms^{-2}, $p=0.04$). Dietary nitrate had no impact, but did rise in plasma.
Spironolactone improved Δrelative wall thickness vs. doxazosin (0.01[-0.02,-0.0], $p<0.01$). Dietary nitrate decreased left ventricular (LV) end diastolic and systolic volume (-6.3[-11.1,-1.6]mL and -3.2[-5.9,-0.5]mL, $p<0.05$) and increased end diastolic mass/volume (EDMV) ratio (0.04 [0,0.7] g/mL, $p<0.05$) vs. placebo. There were no drug—juice interactions.
Conclusions: Contrary to our hypothesis, spironolactone did not reduce AS, rather central PWV declined on doxazosin. Spironolactone enhanced LV remodelling, while dietary nitrate improved LV volumes and the EDMV ratio, perhaps indicating improved LV strain.

3.2
VARIABILITY IN MEAN ARTERIAL PRESSURE AND DIASTOLIC BLOOD PRESSURE FROM CENTRAL TO PERIPHERAL LARGE ARTERIES: RELEVANCE TO ARTERIAL PHYSIOLOGY AND ESTIMATED CENTRAL BLOOD PRESSURE

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Background: Mean arterial pressure (MAP) and diastolic blood pressure (DBP) are thought to consistently decline approximately 1-3 mmHg from the aorta to peripheral large arteries, thus providing a small pressure gradient to aid blood flow. The magnitude of this gradient is important for correct waveform calibration and central BP estimation. However, there is little invasive data determining the variability in MAP and DBP from central to peripheral arteries, which was the goal of this study.
Methods: 52 patients (mean age 62$\pm$11 years) undergoing cardiac angiography had intra-arterial BP measured via catheter in the ascending aorta, brachial and radial arteries by sequential pull-back. MAP was calculated by integration of ensemble averaged waveforms, and DBP from the foot of the waveforms.
Results: On average, MAP and DBP decreased from the aorta-to-brachial (MAP -1.5$\pm$3.9 mmHg DBP -2.7$\pm$4.1 mmHg) and brachial-to-radial (MAP -2.0$\pm$4.4 mmHg DBP -1.8$\pm$3.3 mmHg) arteries. However, changes in aortic-to-radial MAP (range -14.9 to 6.8 mmHg) and DBP (range -13.1 to 2.1 mmHg) were highly variable, including increases in MAP among 23% of patients. Importantly, the relationship between MAP and DBP changes were synergistic, with DBP decreasing if MAP increased and vice versa. The magnitude of aorta-to-radial MAP and DBP differences were significantly related to height and age.
Conclusions: Although MAP and DBP are reduced on average from central to peripheral large arteries, the magnitude of change is variable and related to patient characteristics. These new observations are highly relevant to understanding arterial hemodynamic (patho)physiology and accurate non-invasive estimates of central BP.

3.3
DISCOVERY OF A NEW BLOOD PRESSURE PHENOTYPE FROM INVASIVE CENTRAL-TO-PERIPHERAL RECORDINGS: IMPLICATIONS FOR BRACHIAL CUFF ACCURACY AND CARDIOVASCULAR RISK ASSESSMENT

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Background: Accuracy of brachial cuff blood pressure (BP) may be influenced by individual variability in central-to-peripheral systolic BP (SBP)-amplification, but this has never been determined. We aimed to achieve this by characterising SBP-amplification phenotypes and examining associations with cuff BP accuracy.
Methods: Intra-arterial BP was measured at the ascending aorta, brachial and radial arteries in 77 patients (aged 61.5$\pm$10.3 years 68% male) following coronary angiography. Cuff BP was measured bilaterally by oscillometric devices before catheterisation, and then simultaneously with intra-arterial brachial BP. SBP-amplification was defined by $\geq$5 mmHg SBP increase between the aorta-to-brachial or brachial-to-radial arteries.
Results: Average aortic-to-brachial and brachial-to-radial SBP-amplification were 8.5$\pm$9.5 mmHg and 6.4$\pm$9.4 mmHg respectively. However, four distinct SBP-amplification phenotypes were observed: 1) both aortic-to-brachial and brachial-to-radial SBP-amplification ($n=24$) 2) only aortic-to-brachial SBP-amplification ($n=24$) 3) only brachial-to-radial SBP-amplification ($n=16$) 4) no aortic-to-brachial or brachial-to-radial SBP-amplification ($n=13$). Compared with the first three phenotypes, patients with no SBP-amplification had elevated aortic SBP (143.1$\pm$23.0 mmHg versus 122.4$\pm$18.3 126.0$\pm$19.5 and 134.8$\pm$12 mmHg respectively $p=0.0066$) that was significantly underestimated by brachial cuff BP (-11.7$\pm$8.7 mmHg, $p=0.004$), despite no differences in clinical characteristics or cuff BP between phenotypes ($p>0.1$ all).
Conclusions: These are the first data to describe distinctive central-to-peripheral SBP-amplification phenotypes, and includes discovery of a phenotype in which cardiovascular risk is likely to be elevated because of significantly increased aortic SBP that is not detected by conventional cuff BP methods.

3.4
WAVE INTENSITY ANALYSIS PROVIDES NOVEL INSIGHTS INTO PULMONARY HYPERTENSION

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Background: The objective of the study was to apply wave intensity analysis (WIA) in the pulmonary artery to characterise the magnitude, origin, type and timing of arterial waves in individuals with and without pulmonary hypertension (PH).
Methods: Right heart catheterisation was performed using a pressure and Doppler flow sensor tipped catheter to obtain simultaneous pressure and

flow velocity measurements in the pulmonary artery. WIA was applied to the acquired data (1).
Results: In controls (n = 10), the wave speed in the pulmonary artery was 3.03 m/s (2.69 − 3.91 m/s) and this increased in pulmonary arterial hypertension (PAH, n = 11, 11.9 m/s [10.5 − 16.4 m/s]) and chronic thromboembolic pulmonary hypertension patients (CTEPH, n = 10, 15.1 m/s [11.5 − 16.8 m/s]). Wave intensity was significantly greater in PH patients compared to controls. Wave reflection index (WRI) was 3.81 % (3.58 − 6.24 %) in controls, 23.4 % (17.5 − 29.7 %) in PAH and 30.4 % (11.9 − 35.6 %) in CTEPH patients. WRI was not related to pulmonary vascular resistance or right ventricular fractional area change and patients with mildly and severely elevated pulmonary pressure had similar WRI.
Conclusions: Wave speed, wave intensity and wave reflection in the pulmonary artery was higher in PH patients indicating increased arterial stiffness, right ventricular work and vascular impedance mismatch, respectively. While WRI does not reflect the severity of PH in established disease, the presence of increased wave reflection could be a novel early marker of pulmonary vascular disease.
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3.5
NON-INVASIVE US-BASED WAVE INTENSITY ANALYSIS IN MICE

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Wave Intensity Analysis (WIA) can provide information about the interaction between vascular and cardiac system. WIA-derived indexes have quantitative physiological meaning. We investigated age-associated changes in WIA-derived parameters in mice and correlated them with biomarkers of cardiac function.
Sixteen wild-type male mice (strain C57BL6) were imaged with high-resolution ultrasound (Vevo 2100) at 8 weeks (T0) and 25 weeks (T1) of age. Carotid pulse wave velocity (PWV) was calculated from B-Mode and PW-Doppler images using the lnD-V loop and employed to evaluate WIA: amplitudes of the first (W1) and the second (W2) local maxima and minimum (Wb) were assessed. Reflection index (RI) was assessed as Wb/W1. Cardiac output (CO), ejection fraction (EF) fractional shortening (FS) and stroke volume (SV) were evaluated strain analysis provided strain and strain rate values for longitudinal, radial and circumferential directions (LS, LSR, RS, RSR, CS, CSR). Isovolumetric relaxation time (IVRT) was calculated from mitral inflow PW-Doppler images and normalized for cardiac cycle length.
W1(T0:4.42e-07±2.32e-07m2/s T1:2.21e-07±9.77e-08m2/s), W2(T0:2.45e-08±9.63e-09m2/s T1:1.78e-08±7.82e-09m2/s), Wb(T0:-8.75e-08±5.45e-08m2/sT1:-4.28e-08±2.22e-08m2/s), CO(T0:19.27±4.33ml/min T1:16.71±2.88ml/min), LS(T0:17.55±3.67% T1:15.05±2.89%), LSR(T0:6.02±1.39s-1 T1:5.02±1.25s-1), CS(T0:27.5±5.18% T1:22.66±3.09%) and CSR(T0:10.03±2.55s-1 T1:7.50±1.84s1) significantly reduced with age. W1 was significantly correlated with CO(R=0.58), EF(R=0.72), LS(R=0.65), LSR(R=0.89), CS(R=0.61), CSR(R=0.70) at T0; correlations were not significant at T1.!
The decrease in W1 and W2 suggests a reduction in cardiac performance, while that in Wb, in view of unchanged RI, can be associated with a reduction in the total energy carried by the wave. The loss of correlation between WIA-derived parameters and cardiac biomarkers might reflect an age-associated alteration in cardio-vascular coupling.

3.6
LONGITUDINAL CHANGES IN AORTIC RESERVOIR FUNCTION INDEPENDENTLY PREDICT DECLINING RENAL FUNCTION AMONG HEALTHY INDIVIDUALS

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Objectives: Aortic reservoir function independently predicts end organ damage in cross sectional analyses. However, longitudinal associations are more important regarding causation, but this has never been examined and was the goal of this study.
Methods: Aortic reservoir function (excess pressure integral [xsP] and aortic reservoir pressure), aortic stiffness, brachial and central blood pressure (BP), and renal function (estimated glomerular filtration rate [eGFR]) were recorded among 33 healthy individuals (57±9 years 55% male) at baseline and after an average 3.0±0.3 years.
Results: Over the follow up period there was no significant change in brachial BP ($p>0.05$), whereas there was a trend for xsP ($p=0.061$) and central BP ($p=0.068$) to increase. On the other hand, aortic stiffness and blood glucose increased significantly ($p<0.05$ both). The change over time in xsP (but not aortic stiffness) was significantly related to the change in eGFR ($r=-0.370$, $p=0.044$) and this remained independent age, 24 hour systolic BP and body mass index ($\beta=-0.031$, $p=0.045$), but not blood glucose ($\beta=-0.031$, $p=0.053$). There was no interaction between the change in glucose and change in xsP.
Conclusions: Aortic reservoir function, as determined by excess pressure, is independently associated with a decline in renal function among healthy people followed over 3 years. These novel findings indicate the need to determine the underlying physiological determinants of aortic reservoir function.

3.7
ARTERIAL STIFFNESS FOR THE EARLY PREDICTION OF PRE-ECLAMPSIA COMPARED WITH CLINICAL CHARACTERISTICS, UTERINE ARTERY DOPPLER INDICES, AND ANGIOGENIC BIOMARKERS

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Objective: To develop a model for the 1st trimester prediction of pre-eclampsia.
Methods: In this prospective longitudinal study, women with high-risk singleton pregnancies were recruited and arterial stiffness was measured using applanation tonometry (SphygmoCor, AtCor) and compared between women who developed PE and those who had a normotensive pregnancy. Arterial stiffness and hemodynamics were assessed, in the 1st trimester, every 4 weeks thereafter, and at 6 weeks postpartum. Angiogenic biomarker concentrations (Quantikine, R&D Systems) were measured at each trimester and at 6 weeks postpartum, and a bilateral uterine artery Doppler (UAD) was performed in the 2nd trimester.
Results: Of the 155 women recruited, 13 developed pre-eclampsia. Analyses adjusted for both maternal age and body mass index showed women who developed pre-eclampsia had significantly increased wave reflection and carotid-femoral pulse wave velocity (cfPWV) from the 1st trimester, throughout pregnancy, and at 6 weeks post-partum with a cfPWV:carotid-radial PWV mistmatch seen in the 1st and 3rd trimester (all p-values<0.05). Arterial stiffness (AUC: 0.80) was a better predictive tool than angiogenic biomarkers (AUC: 0.60; $p=0.04$) or UAD (AUC: 0.53; $p<0.001$) and improved detection of pre-eclampsia when combined with all other predictions (AS sensitivity: 79.8% vs other combinations' sensitivity: 69.2%).
Conclusions: Arterial stiffness and wave reflection is higher in the 1st trimester, throughout pregnancy, and does not resolve 6 weeks after pregnancy in women who develop pre-eclampsia. It also had superior preeclampsia predictive value over angiogenic biomarkers and UAD alone and improved detection rates when combined with all predictors including clinical characteristics.

3.8
CAN ARTERIAL WAVE AUGMENTATION IN YOUNG ADULTS EXPLAIN VARIABILITY OF CARDIOVASCULAR RISK IN ETHNIC MINORITIES?

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Objective: Traditional cardiovascular (CV) risk factors do not fully explain ethnic differences in CV disease [1,2]. We tested if pulse wave velocity