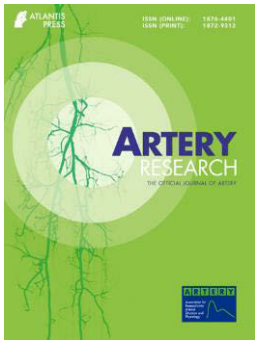

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4.3: WHOLE-BODY VS. REGIONAL ARTERIAL STIFFNESS: IMPLICATIONS FOR A SINGLE WINDKESSEL MODEL OF THE CIRCULATION

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3.8
CHILDHOOD OBESITY: DOES IT HAVE ANY EFFECT ON YOUNG ARTERIES?

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Background: Prevalence of overweight (OW) and obesity (O) in children and adolescents has been increased in the past three decades. Obese children are prone to develop early cardiovascular (CV) morbidity in their adult life. Impaired arterial stiffness might be detected in this population. The aim of our study was to compare the arterial function parameters (AFPs) in O/OW patients and healthy subjects.
Methods: 6.816 subjects (3.668 boys) aged 3—18 years were recruited and categorised by their body mass index (BMI) into normal weight (N), OW and O groups regarding their age and sex. AFPs were measured by occlusive-oscillometric device. Propensity score matching was carried as statistical test.
Results: 19.9% (n = 1.356) of the population were OW/O, 911 (516 boys) were OW and 445 (273 boys) were O. PWVao did not differ significantly between N (5.9 ± 0.8 m/s) and OW patients (5.9 ± 0.8 m/s); and N (6.0 ± 0.7 m/s) and O patients (6.0 ± 0.8 m/s). Aixao was significantly lower in OW (9.3 ± 7.4% vs 7.6 ± 7.0%, $p < 0.00001$) and in O patients (9.7 ± 8.1% vs 6.6 ± 7.2%, $p < 0.00001$) compared to controls. No significant difference was found regarding SBP_{ao} values between controls and OW and O groups (N = 110.7 ± 12.4 mmHg vs OW = 110.3 ± 11.9 mmHg; N = 115.6 ± 14.0 mmHg vs O = 114.3 ± 12.8 mmHg).
Conclusions: Aortic stiffness — expressed by PWV_{ao} — did not differ between N and O/OW children and adolescents, however Aix_{ao} was remarkably, significantly lower in O/OW patients. We may conclude that the pathophysiological consequences in the circulatory system due to childhood OW/O are compensated hemodynamically in these patients, presumably by decreasing total peripheral vascular resistance.

Oral Session IV — Models, Methodologies and Interventions

4.1
PROBING ARTERIAL STIFFNESS AT THE NANO-SCALE USING THE INTERNAL MAMMARY ARTERY AS A NOVEL TARGET

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Introduction: Arterial stiffening is associated with structural and biomechanical alterations in the aorta. However, there are still gaps in our understanding as to how the structure and properties of arteries across the vasculature are altered with high PWV.Objective: To determine whether altered ultrastructural and nanomechanical properties are exhibited in the internal mammary artery (IMA) in high PWV patients.
Methods: Human IMA biopsies were obtained from patients with known carotid-femoral PWV. Patients were grouped as low PWV (8.5 ± 0.7 ms^{-1}, n = 8) and high PWV (13.4 ± 3.0 ms^{-1}, n = 9). With Peakforce QNM atomic force microscopy (AFM) the nanomechanical (elastic modulus) and morphological properties (collagen fibril diameter and D-Period) of the IMA were measured. Principal component analysis (PCA) was used to determine the relationship of nanomechanical and structural data with proteomics data (small leucine rich proteoglycans, SLRPs) [1] and patient metadata.
Results: PCA analysis shows that the nano-scale elastic modulus was one of the key variables which separated low and high PWV groups and was correlated with PWV. Furthermore, nano-scale alterations in adventitial collagen fibrils were evident. D-Period and collagen fibril diameter were found to be negatively correlated. Most SLRPs were closely grouped in the PCA analysis.
Conclusions: Although the IMA is not involved in the carotid-femoral pathway, patients with high PWV exhibited distinct alterations in the IMA at the nano-scale relative to those with low PWV. Our approach provides new insight into systemic structure-property changes in the vasculature, and also provides a novel method for characterizing small biopsy samples for arterial stiffening studies.

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4.2
DISCREPANCY BETWEEN IN-VIVO MEASURE AND EX-VIVO CALCULATION OF PULSE WAVE VELOCITY IN RETINAL ARTERIES

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Background: Pulse wave velocity (PWV) in large arteries is a pressure-dependent marker of arterial stiffness. The retinal vasculature provides unique access to the microcirculation. There is inconsistency between reported values of retinal PWV (rPWV). The pressure dependency of rPWV was measured in-vivo and calculated ex-vivo using retinal artery material properties to investigate the inconsistencies.
Methods: High-speed fundus videos (125 fps) from three Sprague Dawley rats were recorded simultaneously with electrocardiogram and blood pressure. rPWV was measured using the cardiac component of retinal artery diameter waveforms at two retinal sites across a physiological range (70—130 mmHg) of mean arterial pressure (MAP). Ex-vivo tensile testing was performed on bovine retinal arteries, rat retinal arteries being too small for myography. Diameter and wall thickness of the retinal artery adjacent to the optic disc were measured using optical coherence tomography. Tensile testing was performed using a wire myograph in 9 bovine retinal artery specimens.
Results: In-vivo results showed a significant positive correlation between rPWV (4.9 ± 1.8 mm/s) and MAP ($R2 = 0.58$, $p < 0.001$) as expected. *Ex-vivo*, calculated rPWV using material stiffness and geometry measurement ranged between 4.6 and 7.0 m/s at effective distending pressures between 70 and 100 mmHg.
Conclusions: *Ex-vivo* and *in*-vivo results differed by three orders of magnitude but should be the same. *Ex-vivo* results are in the same order as measured *in-vivo* in large arteries. *In-vivo* rPWV was lower than expected yet was responsive to changes in MAP. Further studies are required to uncover what rPWV is a measurement of, if not arterial stiffness.

4.3
WHOLE-BODY VS. REGIONAL ARTERIAL STIFFNESS: IMPLICATIONS FOR A SINGLE WINDKESSEL MODEL OF THE CIRCULATION

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Introduction: We questioned whether a single Windkessel (WK) adequately describes the circulation by estimating the radial arterial diastolic pressure-decay constant (tau) and combining this with systemic hemodynamic and arterial stiffness measurements.
Methods: In the non-invasive cardiac laboratory, we performed echocardiography with simultaneous cuff BP, heart-femoral [hf] and femoral-ankle [fa] PWV (Colin VP1000), and radial tonometry (Sphygmocor). Tau was calculated by photo-digitizing the radial pulse contour and fitting pressures (at 20 ms intervals) to: P = A + ([systolic BP]-A)*exp(-(t-t0)/tau), where P = pressure, A = modeled minimum diastolic BP, and t0 = mono-exponential decay start time. Systemic vascular resistance (SVR) = mean pressure/[cardiac output]; WK stiffness (1/[WK capacitance]) = SVR/tau; central and peripheral

arterial stiffness = hfPWV 2 and faPWV 2 , respectively; and estimated wall/lumen ratio (W/L) = PWV 2/(central pulse pressure/stroke volume).
Results: In 76 individuals (mean age 55 years, weight 84 kg, BP 138/79 mmHg, resting HR 67; 45% female), WK stiffness was negatively correlated with age($p<0.05$) but not with BP, $hfPWV^2$ or $faPWV^2$. In contrast, $hfPWV^2$and $faPWV^2$ were positively correlated with age ($p<0.0001$ and $p<0.01$, respectively) but neither was correlated with tau or WK stiffness. Using 6 multilinear stepwise backward regression models for WK stiffness, the major contributing factors were: SVR ($p<10^{-6}$), t0 ($p<10^{-6}$), heart rate ($p<10^{-5}$), and W/L ($p=0.01$).
Conclusion: We identified SVR, heart rate, timing of pressure decay, and vessel geometry as correlates of WK stiffness but the lack of relationship between PWV-based arterial stiffness and stiffness derived from the WK model mitigates against a single arterial WK.

4.4
CAN LASER DOPPLER VIBROMETER DETECT CAROTID STENOSIS FROM SKIN VIBRATIONS? HYDRAULIC BENCH TESTS ON PATIENT-SPECIFIC MODEL

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Background: Within the H2020 CARDIS project, we explore the use of a Laser Doppler Vibrometer (LDV) [1] to detect asymptomatic carotid stenosis from measurement of skin vibrations on the neck of affected patients. We hypothesise that flow instabilities induced by the stenosis will propagate as mechanical waves through soft tissues of the neck. We here report measurements on an experimental model to assess the ability of LDV to detect stenosis-induced vibrations.
Methods: A compliant carotid bifurcation with Internal Carotid Artery (ICA) 76% area-stenosis model was surrounded by hydrogel and a skin-like layer to mimic neck's skin and soft tissues. Measurements were acquired (20 KHz) at physiological flows (water) through the artery [2, 3], at several distances downstream from the stenosis. Intra-arterial pressure measurements were performed at the same location for reference (Fig. 1A). To assess in which frequency range the Fast Fourier Transform spectra of the signals are most sensitive to changes in flow rate, we constructed a univariate linear model in SPSS for the integral of the normalized spectra (8K, Hann, 50%-overlap, LabChart), where inflow was used as covariate and the frequency range as fixed factor.
Results: The spectrograms (Fig1B) showed that the LDV was able to detect flow-induced instabilities in the 0—500 Hz range. The sensitivity was highest between 50—150 Hz for both LDV and pressure.
Conclusion: The LDV was able to detect stenosis-related flow features with a sensitivity comparable to the intra-arterial manometer, proving the potential of the technique for stenosis diagnosis by detecting neck skin vibrations. In-vivo validation is in progress.

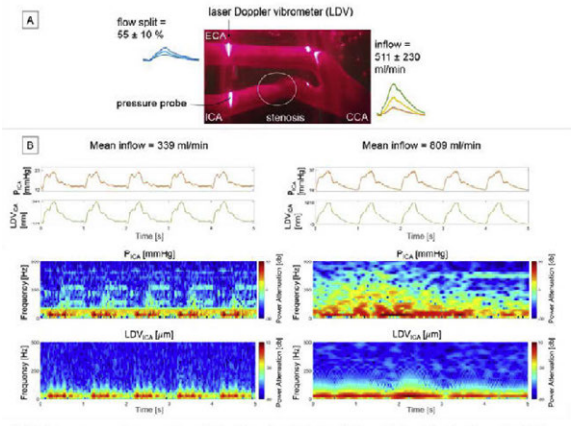

Fig1A: The pressure probe was positioned in the internal carotid artery (ICA) and the laser Doppler vibrometer (LDV) on the surface directly above the pressure probe. Panel B: pressure and LDV signals in the ICA, and their spectrograms (1K, Hann, 93%-overlap, LabChart). The amplitude of the disturbances was greater at a higher mean inflow for both signals.

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4.5
CARDIAC OUTPUT ESTIMATION FROM BEAT-TO-BEAT RADIAL PRESSURE AND PULSE WAVE VELOCITY: A MODEL-BASED STUDY

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Background: Cardiac output (CO) monitoring remains a salient challenge. The state-of-the-art is based on generalized transfer functions and parameter estimations from pooled clinical data, which do not necessarily reflect the state of the cardiovascular system in a patient-specific way. Here, we introduce a patient-specific approach to estimate CO from sequential radial pressure measurements and carotid-to-femoral pulse wave velocity (cf-PWV). We do so by effectively tuning a generalized mathematical model of the cardiovascular system (1).
Methods: Initially, the method uses the measured cf-PWV to estimate arterial compliance. We consequently determine aortic flow from beat-to-beat radial pressure measurements based on the assumption of a fairly constant total peripheral resistance (TPR) over several heartbeats (2). Concretely, we developed an algorithm which, starting from an initial flow, employs a gradient-based optimization process (3) to calculate TPR at each beat. This TPR value is subsequently used as input for a new flow approximation. The process is repeated until convergence is reached. To assess the accuracy of the method, we implemented the algorithm on in vivo anonymized data from $n=15$ subjects (4) and compared the method-derived CO to the measured ones.
Results: Our results demonstrated that precise estimates of CO were yielded, with a RMSE of 0.38 L/min (Fig. 1). Small variance in arterial compliance tuning did not show to significantly undermine the accuracy of the CO predictions.
Conclusions: The in vivo validation allows us to conclude that our novel method accurately estimates CO in a patient-specific way. Therefore, the technique may potentially be employed for noninvasive CO monitoring in the clinical setting.

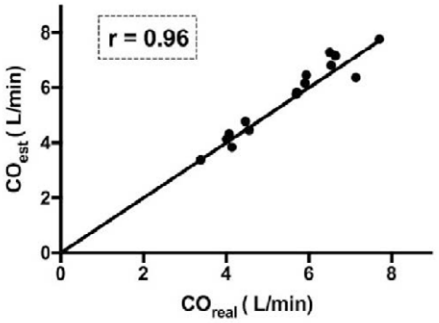

Fig.1. Scattergram of model-derived CO estimates vs. *in vivo* CO data

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