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2.4: SERUM BIOMARKERS AND RETINAL VESSEL DIAMETERS IN SCHOOL CHILDREN

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MRI. Strokes were identified from primary care record review and hospital discharge data.

Results. Stroke was most frequent in AfC. Prevalence of infarcts was similar in all ethnic groups while WMH were most frequent in AfC. Mean carotid IMT (excluding those with plaque) was greatest in AfC. (Table) CAC was greater in WE and SA. In WE, associations between carotid IMT and presence of stroke, infarcts or WMH was strong, even after adjustment for Framingham risk factors and CAC (fully adjusted odds ratio (OR(95%CI)) for a 1 SD increase in IMT:1.34(1.10, 1.64)). However, in SA and AfC there was little association between IMT and CVD (fully adjusted ORs: 1.12(0.87, 1.44), 0.74 (0.51, 1.08) respectively (ethnicity x IMT interactions: $P = 0.32$ and 0.028 respectively). CAC was independently associated with CVD in WE (fully adjusted OR for 10 unit increment:1.003(1.0004, 1.001), but less so in SA (1.002(1.00, 1.005) or AfC (1.00(0.99, 1.006)).

Conclusion. Neither carotid IMT nor CAC were independently associated with presence of clinical and subclinical cerebrovascular disease in South Asians or African Caribbeans. In Europeans, IMT was more strongly associated than CAC.

*Median (IQR)	White Europeans	South Asians	African Caribbeans
Number	630	484	217
Male	77%	86%	52%
Smoking (never/ex/current)	38/54/8%	78/18/4%	66/28/6%
Treated hypertension	56%	76%	79%
Total cholesterol: HDL ratio*	3.5(2.9, 4.2)	3.4(2.8, 4.2)	3.2(2.6, 3.8)
Waist:hip ratio*	0.97 (0.93, 1.02)	1.00 (0.96, 1.04)	28.4 (25.6, 31.9)
CAC, AU*	97(6,384)	92(7,410)	0.95 (0.90, 1.01)
CIMT, mm*	0.88 (0.76,1.04)	0.89 (0.79,1.02)	0.92 (0.81,1.04)
Carotid lumen diameter, mm	6.61 ± 0.87	6.44 ± 0.76	6.20 ± 0.78
Stroke	4%	5%	9%
Brain infarcts, any (MRI)	21%	20%	22%
White matter hyperintensities	33%	30%	42%
Presence of any stroke, infarcts, WMH	37%	37%	47%

2.2

TRANSFER FUNCTION-DERIVED CENTRAL PRESSURE AND CARDIOVASCULAR EVENTS: THE FRAMINGHAM HEART STUDY

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Relations between central versus brachial blood pressure and major cardiovascular disease (CVD) events remain controversial. Central measures derived using radial tonometry and a generalized transfer function as implemented using the SphygmoCor device may better predict CVD risk compared to central pressures from carotid tonometry. We used proportional hazards models to examine relations of augmentation index, central systolic and pulse pressure, and central-to-peripheral pulse pressure amplification obtained using the SphygmoCor algorithm to first-onset major CVD events in 2183 participants

(mean age 62 years, 58% women) in the Framingham Heart Study. During median follow-up of 7.8 (range 0.2 to 8.9) years, 149 participants (6.8%) had an incident event. Augmentation index ($P = 0.6$), central systolic pressure ($P = 0.20$), central pulse pressure ($P = 0.24$) and pulse pressure amplification ($P = 0.15$) were not related to outcomes in models that adjusted for age, sex, clinic systolic blood pressure, use of antihypertensive therapy, total and high density lipoprotein cholesterol concentrations, smoking, and presence of diabetes. When models were repeated using supine oscillometric systolic pressure recorded at the time of tonometry and excluding cases with tonometry pulse height variations >5%, pulse diastolic variation >5%, pulse shape variation >4% or an operator index <80, as recommended by SphygmoCor documentation ($N = 1262$, 64 events), central pulse pressure estimated using the SphygmoCor algorithm was inversely associated with events ($HR = 0.64$, confidence limits 0.42 to 0.98; $P = 0.04$). After considering standard risk factors including brachial systolic pressure, higher central pressure derived using radial artery tonometry and a generalized transfer function was not associated with higher CVD risk.

2.3

PULSE WAVE VELOCITY IN A LARGE POPULATIONAL STUDY. PRELIMINARY RESULTS BRAZILIAN LONGITUDINAL STUDY OF ADULT HEALTH (ELSA-BRASIL)

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Large artery stiffening is widely accepted as a determinant of ISH in the population with a predictive power of CV events has been shown to be beyond traditional risk scores. However, its clinical role in is still limited perhaps due to the lack of established reference values and methodological uniformity. The aim of this prospective longitudinal study is to investigate the role of large artery stiffening as determinant of cardiovascular disease. ELSA-Brazil is a cohort study of 15,105 university servants, aged 35-74 years. The baseline examination was carried out from 2008 through 2010 and included interviews, clinical, anthropometric examinations, overnight urine, ECG, IMT, echocardiography, retinography, HR variability, and PWV (Complior). All centres were submitted to a central training and validation. A biologic sample was stored to allow investigation of biomarkers of CV risk. Values are mean ±SD. PWV measurements were obtained in 14,835 individuals (M:F; 6,780:8,055). PWV is strongly influenced by age and BP ($R^2 = 0.41$). HR and fasting glucose provides only additional 2% in R^2 change. Lipids were not correlated to PWV. Age and BP adjusted values in men are higher than in women (9.53 ± 1.89 vs 9.2 ± 1.88 m/s, $P < 0.001$), but the slope of correlation with age are not different. BP status does not change the correlation of BP and PWV. However adjusted PWV values are increased in Diabetic individuals (9.97 ± 2.3 vs $9.18 \pm m/s$, $P < 0.001$). The present study has a potential to clarify important questions regarding the role of PWV as a determinant of disease, favouring its routine inclusion in clinical practice.

2.4

SERUM BIOMARKERS AND RETINAL VESSEL DIAMETERS IN SCHOOL CHILDREN

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Objectives. Retinal vessel analysis is a valid diagnostic tool to detect sub-clinical signs of atherosclerosis in the cerebrovascular microcirculation as early as childhood. The aim of the study was to investigate the association between specific obesity-related biomarkers and retinal vessel diameters in school children.

Methods. We studied 381 children aged 10 to 13 years in a school-based setting. Anthropometric measurements and blood sampling were conducted using standard protocols for children. The serum biomarkers leptin, insulin, adiponectin and IL-6 were assessed and correlated with retinal arteriolar (CRAE) and venular (CRVE) diameters and the arteriolar-to- venular ratio

(AVR). Retinal vessel analysis was performed by use of a non-mydratric vessel analyser (SVA-T) using a computer-based program.

Results. Overweight and obese children had higher leptin and insulin levels and reduced adiponectin levels compared to normal weight children ($p < 0.05$). IL-6 levels were significantly higher in obese children compared to normal weight peers ($p < 0.001$). Wider CRVE ($p = 0.031$) and lower AVR ($P = 0.01$) were associated with higher leptin levels. Insulin levels were associated with arteriolar as well as venular dilatation depending on confounder adjustment.

Conclusions. All of the above serum risk factors are altered in childhood obesity. However, only leptin and insulin levels are associated with retinal vessel diameter changes, a cumulative microvascular biomarker. Intervention studies are warranted to examine whether lifestyle improvements can prevent alterations of the vasculature early in life.

2.5

AORTIC-BRACHIAL STIFFNESS MISMATCH AND MORTALITY IN DIALYSIS PATIENTS

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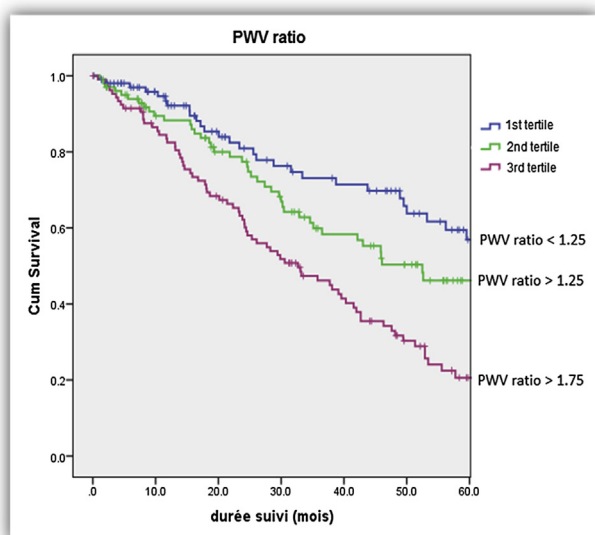
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Objective. We have shown that regression of brachial stiffness is inversely related to aortic stiffness in dialysis patients. In this study, we sequentially examine the impact of aortic stiffness, brachial stiffness and aortic-brachial stiffness mismatch on mortality in dialysis patients.

Design and Method. This is a prospective longitudinal study conducted in 310 adult dialysis patients (mean age 65 ± 15). Aortic and brachial stiffness were respectively measured by determination of carotid-femoral (cf-PWV) and carotid-radial pulse wave velocity (cr-PWV) (CompliorSP-direct measurement technique). Aortic-brachial stiffness mismatch was defined by cf-PWV/cr-PWV mismatch. Central pulse wave profile was determined by radial applanation tonometry. After a mean follow-up of 3.6 ± 1.7 years mortality status was assessed. ROC curve analysis was performed to evaluate the impact of central pulse pressure (PP), heart rate adjusted augmentation index (Aix), cf-PWV, cr-PWV and the cf-PWV/cr-PWV ratio on mortality.

Results. The cf-PWV was 13.5 ± 4.1 m/s, cr-PWV was 8.7 ± 1.7 m/s, cf-PWV/cr-PWV ratio was 1.6 ± 0.5 , central PP was 49 ± 21 mmHg and the Aix $26.8 \pm 11.1\%$. During follow-up, 160 (49%) deaths occurred. Area under the curve was largest for cf-PWV/cr-PWV ratio (0.694, $p < 0.001$), followed by cf-PWV (0.627, $p < 0.001$), Aix (0.617, $p < 0.001$), PP (0.598, $P = 0.003$) and cr-PWV (0.371, $p < 0.001$). Figure 1 shows patient survival according to tertiles of aortic-brachial stiffness ratio. In univariate and various adjusted models using Cox regression model, aortic-brachial stiffness was independently associated with increased risk of mortality.

Conclusion. Aortic-brachial stiffness mismatch was better than aortic stiffness alone in predicting clinical outcome in this population.



2.6

THE NONLINEAR COMPONENTS OF PULSE PRESSURE: NOVEL MARKERS FOR ARTERIAL STIFFENING WITH PROGNOSTIC SIGNIFICANCE

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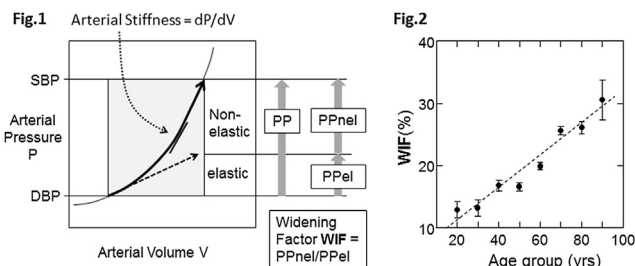
Mean ambulatory pulse pressure (PP) is a potent predictor of cardiovascular and all-cause mortality.

Objectives. Investigating prognostic significance of elastic and non-elastic PP components

Methods. Using a generalized nonlinear pressure–volume relationship in arteries (Fig. 1), PP can be split into an elastic component (PPel) with constant (diastolic) arterial stiffness and a non-elastic component (PPnel) that reflects arterial stiffening during the systole. We determined PPnel, PPel and the ratio WIF = PPnel/PPel ('Widening Factor') from 24-hour ambulatory BP measurements (ABPM) using a model. Standardized hazard ratios (HR) were estimated with Cox proportional hazards regression adjusted to age, gender, body mass index, mean arterial pressure, heart period (HP), systolic- and heart rate-dipping and diabetes and medication status. Assuming an exponential P-V relationship, the model provides the expression $WIF = [(K-1)/\ln(K)] - 1$, where $K = SD(SBP)/SD(DBP)$ (SD = standard deviation) and $PPel = PP / (1 + WIF)$

Results. ABPM records of 2,105 individuals followed for 5 years for all-cause mortality were analyzed (age 56 ± 16 , 55% women, 60% on medication and 9% diabetes, 115 died). Predictive power was demonstrated for patients with slower-than-median pulse rate ($HP > 0.87$ s, $n = 78$): Mean(95%CI) HR of PPnel and WIF were 1.46(1.13-1.90) and 1.64(1.16-2.33) ($P < 0.005$), respectively, and 1.59(1.21-2.1) and 1.83(1.27-2.63) ($P = 0.001$) for its sub-population of older-than-median-age (> 58 y, $n = 73$). The corresponding HR for PP was 1.34(1.03-1.75) ($P = 0.03$) and 1.53(1.15-2.03) ($P = 0.004$), respectively. PPel did not display predictive power. Fig. 2 shows that WIF varied strongly with age

Conclusion. The 24-hour non-elastic PP component and the Widening Factor, which reflects arterial stiffening during the systole, are novel predictors for mortality, especially in elderly patients with slower pulse.



2.7

A HEALTH ECONOMIC EVALUATION ON THE COST EFFECTIVENESS OF HYPERTENSION MANAGEMENT GUIDED BY CENTRAL BLOOD PRESSURE MEASUREMENT: ANALYSIS OF THE BPGUIDE STUDY

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Objectives. The BPGUIDE study was a prospective, blinded-endpoint study in 286 hypertensive patients randomised to treatment decisions guided by best-practice usual care ($n = 142$) or in addition by central BP measurement ($n = 144$; using SphygmoCor) over twelve months. This study aimed to undertake a health economic assessment to determine cost-effectiveness of hypertension management guided by central BP.

Methods. The primary finding of BPGUIDE was that significantly ($p < 0.001$) less antihypertensive medication was used to achieve BP control in patients randomised to central BP guided care. The savings from these reductions in medications were used to determine the cost-effective fee for service and this amount was then compared to the actual financial cost of central BP measurement in order to gauge financial viability.

Results. Decreases in 5 antihypertensive medication classes over time were used to calculate financial savings using the Australian Government's Pharmaceutical Benefits Scheme dollar costs. Savings from less use of medications was calculated at \$28 to \$32/person (each 3 months) using a capital base cost of \$10,000 (for the SphygmoCor device), 5 years capital life, 5% discount rate, patient throughput of 50/year and, labour costs up to \$250/