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### **2.3: CLINICALLY APPLICABLE APPROACH TO DISCRIMINATE BLOOD PRESSURE DEPENDENT AND INDEPENDENT CHANGES IN ARTERIAL STIFFNESS**

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chromatography/mass spectrometry and untargeted metabolomics profiling were used to identify metabolites (endogenous and/or drug metabolites) that were significantly different after spironolactone treatment compared with placebo.

**Results:** Spironolactone significantly reduced aortic PWV ( $P=0.047$ ), but this change was no longer significant after adjustment for the change in daytime systolic BP ( $P=0.132$ ). Metabolomics profiling identified 43 features (nothing endogenous) that corresponded to downstream spironolactone metabolites, including canrenoate, but none of these correlated with the change in aortic PWV ( $P>0.05$  for all). However, canrenoate was significantly related to the reduction in daytime systolic BP ( $r=-0.355$ ,  $P=0.017$ ) and 24 hour PP ( $r=-0.332$ ,  $P=0.026$ ). These associations remained significant on multiple regression analysis after adjustment for sex and body mass index.

**Conclusions:** The downstream spironolactone metabolite canrenoate appears to be an active metabolite with BP-dependent effects on the attenuation of aortic stiffness in people with HRE. This finding, together with the lack of change in endogenous metabolites relating to fibrosis, suggests that the antifibrotic effects of spironolactone could be BP-dependent.

## Oral session 2

### Free Communication Oral Presentations

#### In association with the North American Artery Society

### 2.1

#### WALL TENSILE STRESS BUT NOT ATHEROSCLEROTIC RISK FACTORS PREDICTS 3-YEAR CAROTID INTIMA-MEDIA THICKNESS PROGRESSION RATE IN HEALTHY SUBJECTS

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Increase in carotid IMT is considered marker of early atherosclerosis. However, experimental and clinical studies suggest that changes in arterial wall thickness may also represent an adaptive response to chronic changes in vessel diameter and/or intraluminal BP aimed to normalize wall tensile stress (WTS).

**Aim of the study:** to assess whether in healthy young-to middle-aged population a short-term common carotid (CCA) IMT progression rate ( $\Delta$ IMT) is associated with WTS at baseline.

**Methods:** study population consisted of 749 healthy subjects at low-average Framingham risk (327 men, age =  $45 \pm 8$  years) undergoing carotid US, fasting blood test (LDL- and HDL-cholesterol, triglycerides), oral glucose tolerance test and questionnaire regarding smoking and family history of cardiovascular diseases at baseline and after 3-year follow-up. WTS was calculated as (diastolic BP \* CCA radius) / IMT.

**Results:** during a 3-year period, BMI, waist girth, systolic and diastolic BP and plasma glucose increased ( $p < 0.001$ ), HR decreased ( $p < 0.001$ ), and plasma lipids and insulin did not change significantly. CCA diameter ( $+0.09 \pm 0.30$  mm,  $p < 0.0001$ ) and IMT ( $+18 \pm 58$   $\mu$ m,  $p < 0.0001$ ) increased, whereas WTS ( $-0.27 \pm 6.70$  kPa,  $p = 0.36$ ) remained unchanged.  $\Delta$ IMT significantly increased by WTS quartiles at baseline ( $p < 0.0001$ ). In multiple regression model, adjusted for gender, smoking, family history and atherosclerotic risk factors (or their 3-year changes), the only independent determinants of  $\Delta$ IMT were male gender, age and WTS at baseline ( $\beta \pm$ SE:  $0.12 \pm 0.04$ ,  $0.17 \pm 0.04$  and  $0.32 \pm 0.04$ , cumulative  $R^2 = 0.20$ ,  $p < 0.0001$ ).

**Conclusions:** In healthy young-to-middle-aged population, the strongest predictor of short-term IMT progression rate was baseline WTS, followed by age and gender. Thus, IMT increase cannot be always considered marker of atherosclerosis.

### 2.2

#### INACCURACIES WITH BRACHIAL AND RADIAL APPLANATION TONOMETRY: SIMILAR IN MAGNITUDE, BUT IN OPPOSITE DIRECTION

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**Background:** It has been postulated that in contrast to the radial artery (RA), brachial artery (BA) tonometry is not capable of accurately acquiring the peaked profile of intra-arterial pressure. We investigated this statement in an invasive study through comparison of the measured form factors (FF).

**Materials and methods:** In 16 subjects (aged 39-82y, 7 males) undergoing an elective coronary angiography, left arm BA and RA pressure waves were recorded invasively (using two high-fidelity tipcatheter pressure wires) and noninvasively (using hand-held applanation tonometry). An average curve per location/technique was constructed. FF was calculated as (mean - min) / (max - min)  $\times$  100. Invasive vs. non-invasive and BA vs. RA data were compared.

**Results:** Form factors and their ratios are shown in the Table as mean  $\pm$  SD.

	invasive	non-invasive	noninvasive/invasive
BA	40.35 $\pm$ 3.20	41.26 $\pm$ 4.84	1.021 $\pm$ 0.062
RA	40.27 $\pm$ 3.11	39.17 $\pm$ 3.75	0.975 $\pm$ 0.082
BA/RA	1.002 $\pm$ 0.033	1.055 $\pm$ 0.090	

In the studied cohort, applanation tonometry tended to overestimate BA FF (i.e. measuring a flattened curve) by 2.1%, yet it also tended to underestimate RA FF (i.e. measuring a more peaked profile) by 2.5%. Combined, these inaccuracies may amplify the BA/RA ratio.

**Conclusions:** Both RA and BA hand-held applanation tonometries introduce inaccuracies of similar magnitude but in opposite direction. These inaccuracies may lead to errors in the assessment of central pressure and brachial-to-radial amplification. Whether these inaccuracies may be improved by investigator-independent automated applanation tonometry should be investigated.

### 2.3

#### CLINICALLY APPLICABLE APPROACH TO DISCRIMINATE BLOOD PRESSURE DEPENDENT AND INDEPENDENT CHANGES IN ARTERIAL STIFFNESS

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**Background:** Monitoring of changes in arterial stiffness in hypertensive patients requires consideration of blood pressure (BP) dependent effects. Based on non-invasive measurements of carotid artery BP and cross-sectional area waveforms, we assessed the BP-dependence change in stiffness in 24 patients referred to our outpatient hypertension clinic, irrespective of antihypertensive treatment.

**Methods and Results:** In 13 women and 11 men (mean  $\pm$  SD; SBP/DBP:  $157 \pm 26 / 92 \pm 10$  mmHg, age:  $53 \pm 15$  yrs, BMI:  $29 \pm 6$  kg/m<sup>2</sup>) tonometric foot-to-foot carotid-femoral pulse wave velocity (cfPWV<sub>f-f</sub>) and common carotid artery cross-sectional area (wall-track) and local pressure waveforms were measured at baseline and at 3-month follow-up. Carotid stiffness was expressed as pulse wave velocity based on the distensibility coefficient (cPWV<sub>DC</sub>). Per individual, a mono-exponential curve was fitted through baseline carotid diastolic (d), dicrotic notch and systolic (s) pressure-area points to enable prediction of the BP-dependent change in stiffness (expressed as cPWV<sub>DC</sub>\*), based on BP values measured at follow-up. In patients in whom diastolic blood pressure (DBP) was significantly reduced, cfPWV<sub>f-f</sub> and (measured) cPWV<sub>DC</sub> were reduced by 1 m/s, similar to the predicted BP-dependent change in stiffness (Table). Patients showing no change in BP showed no change in stiffness. Correlations were: cPWV<sub>DC</sub>\* versus cfPWV<sub>f-f</sub>:  $r = 0.49$  ( $p = 0.020$ ) and cPWV<sub>DC</sub>\* versus cPWV<sub>DC</sub>:  $r = 0.45$  ( $p = 0.037$ ), while cfPWV<sub>f-f</sub> versus cPWV<sub>DC</sub>:  $r = 0.26$  ( $p = 0.22$ ).

**Conclusion:** Quantitative assessment of carotid stiffness as function of pressure enables prediction of BP-dependent changes in stiffness. Our clinically applicable approach could help to discriminate pressure dependent and independent effects of antihypertensive treatment on arterial stiffness.

Table		Changes in predicted* and measured arterial stiffness at 3-month follow up					
		All subjects	p	ΔDBP < -7mmHg	p	ΔDBP > -7mmHg	p
Δ DBP	mmHg	-6 ± 9	0.002	-12 ± 6	< 0.001	1 ± 5	0.40
n		24		14		10	
Δmeds	ddd	1 ± 1	<0.001	2 ± 1	<0.001	0 ± 1	0.18
Δ SBP	mmHg	-14 ± 17	0.001	-24 ± 10	<0.001	1 ± 14	0.83
ΔPP	mmHg	-7 ± 12	0.007	-12 ± 9	<0.001	0 ± 13	0.92
Δ cfPWV <sub>f-f</sub>	m/s	-0.4 ± 1.6	0.29	-1.0 ± 1.5	0.026	0.5 ± 1.4	0.25
Δ cPWV <sub>DC</sub>	m/s	-0.6 ± 1.1	0.021	-1.0 ± 0.8	<0.001	0.1 ± 1.2	0.80
Δ cPWV <sub>DC</sub> *	m/s	-0.6 ± 1.1	0.013	-1.2 ± 0.9	<0.001	0.1 ± 0.8	0.58

Mean±SD. Δmeds denotes antihypertensive medication change, in daily defined dose (ddd). DBP threshold is twice the intrameasurement standard deviation of 3.5 mmHg for DBP.

## 2.4

### VASCULAR AND CARDIAC STRUCTURE AND FUNCTION IN ADULT SURVIVORS OF SEVERE ACUTE MALNUTRITION

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Severe acute malnutrition (SAM) has oedematous or non-oedematous phenotypes and their metabolic effects may persist into adulthood. We hypothesised that cardiovascular structure and function would differ between phenotypes as young adults and between survivors and persons never exposed to SAM.

**Methods:** We recruited 54 non-oedematous and 62 oedematous adult survivors of SAM, and 45 age/sex/BMI-matched community controls. Standardised measures of anthropometry, blood pressure (BP), 2D-echocardiography, carotid and femoral artery ultrasound, brachial, radial and carotid tonometry were performed. Cardiac output (CO), stroke volume (SV), left ventricular mass (LVM) index and outflow tract (LVOT) diameter, carotid and femoral intima-media thickness (IMT), carotid-femoral pulse wave velocity (PWV) and augmentation index were derived. Visceral fat mass was assessed by CT scan. **Results:** Mean (SD) age was 28.8 (7.8) years; 55% were male. Visceral fat mass and BP did not differ significantly between groups. There were no significant differences in cardiovascular measures between oedematous and non-oedematous survivors. After adjusting for age, sex, height and weight, measurements in controls exceeded survivors' expressed in mean (SE) standardized units, as follows: PWV 0.35 (0.14,  $p=0.02$ ), CO 0.53 (0.16,  $p=0.001$ ), LVOT diameter 0.71 (0.16,  $p<0.001$ ), SV 0.44 (0.16,  $p=0.009$ ), and femoral IMT 0.76 (0.19,  $p<0.001$ ).

**Conclusions:** Adult survivors of SAM had less arterial stiffness and decreased CO (due mainly to a smaller SV) compared to controls. The nutritional insult in early childhood may have effects on organ growth and therefore cardiac function. However, at this young age there was no impact on vascular structure and function.

## 2.5

### THE ADDITIVE VALUE OF MEASURING SUBCLINICAL ATHEROSCLEROSIS IS GENDER SPECIFIC

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**Aim:** Cardiovascular disease (CV) risk-stratification could be improved by adding measures of (subclinical) atherosclerosis to current risk scores, especially in intermediate-risk individuals. Our aim was to prospectively evaluate the additive value of non-invasive measurements of atherosclerosis (NIMA) for CV risk-stratification on top of traditional CV risk factors (tCVRF) in a middle-aged population-based cohort.

**Methods:** Carotid plaques, Intima-Media-Thickness (IMT), Ankle-Brachial-Index at rest (ABI-r) and after exercise (ABI-ex), Pulse-Wave-Velocity (PWV), Augmentation-Index (AIx), Central-Augmented-Pressure (CAP), and Central-Systolic-Pressure (CSP) were measured in 1367 CVD-free participants aged 50-70 years. CV-disease (CVD) was evaluated and validated after a mean

follow-up of 3.8 years. The additive value of NIMA on top of tCVRF was evaluated using  $R^2$ , area-under-the-curve (AUC), and net-reclassification-improvement (NRI)-analyses.

**Results:** CVD was reported in 39 men and 32 women. Individual NIMA did not increase  $R^2$  and AUC of the baseline-model (including tCVRF) and additionally showed no substantial reclassification, except for plaque-thickness in women (total-NRI=30.2%,  $p=0.021$ ). In intermediate-risk men, baseline-model was improved by CSP (NRI=20.0%), plaque-thickness (NRI=19.2%), plaque-presence (NRI=16.7%), and ABI-r (NRI=13.6%). In intermediate-risk women all individual NIMA improved baseline-model (IMT showed highest NRI (102%). Combined NIMA improved risk-stratification in all women, and even more in intermediate-risk women. In men, combined NIMA showed additive value in intermediate-risk only. The optimal combinations were PWV-AIx-CSP-CAP-IMT in men (total-NRI=14.5% ( $p=0.087$ ), IDI=0.016 ( $p=0.148$ ), clinical-NRI=46.0%), and IMT-plaque-thickness in women (total-NRI=28.0% ( $p=0.009$ ), IDI=0.047 ( $p=0.061$ ), clinical-NRI=169.2%).

**Conclusions:** In a middle-aged population-based cohort, individual NIMA had additive value on top of tCVRF in intermediate-risk women, and to a lesser extent in intermediate-risk men and could improve CV risk-stratification. Combined NIMA resulted in larger reclassification in both men and women at intermediate-risk, but the optimal combination of NIMA differs between men and women.

## 2.6

### COMPARISON OF HIGH-EFFICIENCY ON-LINE HEMODIAFILTRATION AND HIGH-FLUX HEMODIALYSIS ON VASCULAR FUNCTION AND STRUCTURE IN END-STAGE RENAL DISEASE PATIENTS

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The effects of increasing the convective clearance of uremic toxins using high-efficiency on-line hemodiafiltration (ol-HDF) on vascular function and structure in end-stage renal disease (ESRD) patients remain unknown.

Forty-two ESRD patients were randomized to switch from high-flux hemodialysis (HD) to ol-HDF ( $n=22$ ) or to continue HD ( $n=20$ ) for 4 months in a prospective double-blind study. Brachial artery endothelium-dependent flow-mediated dilatation (FMD), carotid artery structure and stiffness, and cardiovascular coupling, uremic toxins (beta-2 microglobulin, phosphatemia) and circulating markers of inflammation (TNF and inducible NO-synthase blood mRNA) and oxidative stress (reactive oxygen species, total antioxidant status) were assessed at baseline and at follow-up.

FMD increased in patients on ol-HDF ( $152\pm 27$  to  $177\pm 34$  m,  $P=0.002$ ) but not in patients on HD ( $165\pm 46$  to  $161\pm 36$  m,  $P=0.25$ ;  $P<0.01$  vs. ol-HDF). Peripheral and central blood pressures, augmentation index, carotid artery diameter and intima-media thickness remained stable in both groups. Carotid distensibility was higher ( $P=0.04$  vs. HD) and elastic modulus tended to be lower ( $P=0.09$  vs. HD) in patients on ol-HDF. Beta-2 microglobulin ( $P=0.02$ ) and phosphatemia ( $P=0.01$ ) decreased in patients on ol-HDF. Moreover, in patients on ol-HDF, there was a trend for a decrease in inducible NO-synthase ( $P=0.07$ ) and plasma nitrite ( $P=0.06$ ), a marker of NO availability, while TNF increased only in patients on HD ( $P=0.04$ ;  $P=0.01$  vs. ol-HDF). Oxidative stress markers remained stable in both groups.

High-efficiency ol-HDF improves endothelial function and decreases arterial stiffness in ESRD patients as compared with high-flux HD. This may be notably related to the reduction in uremic toxins and vascular inflammation.