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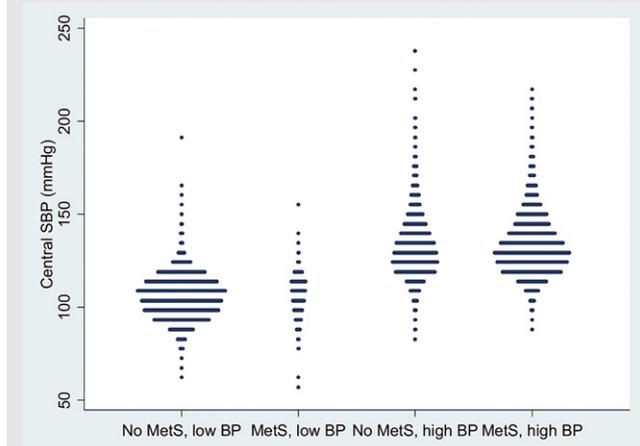
1.6: SPIRONOLACTONE REDUCES AORTIC STIFFNESS IN PEOPLE WITH A HYPERTENSIVE RESPONSE TO EXERCISE VIA THE BLOOD PRESSURE-DEPENDENT EFFECTS OF CANRENOATE

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Table 1 cSBP values stratified by metabolic syndrome and brachial BP status

Conclusions: In these subjects, when adjusting for high normal BP, cSBP is still strongly influenced by the cumulative number of CVRFs. The association between MetS and cSBP is mainly driven by the inclusion of high normal BP in its definition.

1.4

ASSOCIATION OF 24 HOUR AORTIC AMBULATORY BLOOD PRESSURE MONITORING WITH LEFT VENTRICULAR MASS

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Introduction: There is evidence suggesting the superiority of office aortic blood pressure (BP) over office brachial in the management of arterial hypertension. The 24 hour ambulatory blood pressure monitoring (ABPM) is regarded as the optimal method for assessing BP profile; the non-invasive 24 hour aortic ABPM is now feasible.

Objective: To investigate the association and possible superiority of 24h aortic BP over 24h brachial and office BP (aortic or brachial) in the assessment of target organ damage. Non-invasive 24h aortic and brachial ABPM was performed using Mobilo-O-Graph, IEM, a validated brachial cuff based oscillometric device which calibrates the obtained brachial pressure waveform either using SBP and DBP (calib 1) or MBP and DBP (calib 2).

Design and methods: 184 subjects (mean age 55±14 years, 54% male, 48% hypertensives) underwent office brachial (b) and aortic (a) (Sphygmocor) BP assessment, 24h brachial and aortic ABPM and cardiac ultrasound.

Results: The correlation of BP indices with left ventricular mass indexed for body surface area as well as the R square values from multivariate analysis are provided in the table. Using Fisher's z-transformation it was shown that among all SBP parameters only aSBP 24 calib2 had significantly higher correlation coefficient with LVMass compared to office brachial SBP; aSBP calib2 tended to have marginally significantly closer correlation with LVMass than aSBP calib1 (p=0.055).

Conclusion: In the present study 24h aortic SBP calibrated with MBP and DBP seems to be the best alternative to office brachial SBP to assess the association between BP and LVMass.

	Univariate models: Pearson correlation coefficients	Multivariate models (age & gender): R square values
bSBP office (mmHg)	0.293**	0.204
aSBP office (mmHg)	0.286**	0.221
bSBP 24h (mmHg)	0.394**	0.292
aSBP 24h calib 1 (mmHg)	0.338**	0.266
aSBP 24h calib 2 (mmHg)	0.503**	0.347

(**p<0.001 for the provided correlation coefficients)

1.5

BLOOD PRESSURE-INDEPENDENT ASSOCIATION BETWEEN AORTIC CHARACTERISTIC IMPEDANCE AND LEFT VENTRICULAR MASS IN HYPERTENSION

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Background: It is uncertain whether pressure/flow ratio in the proximal aorta, namely aortic characteristic impedance (Z_c), is related to left ventricular (LV) mass independently of blood pressure (BP) level.

Methods: 435 never-treated subjects with uncomplicated essential hypertension free from overt cardiovascular disease (men 62%, age 48±11 years, BP 148/92±16/10 mmHg) underwent M-mode echocardiography and 24-hour BP monitoring. Aortic waveform was obtained from tonometric radial waveform with a validated generalized transfer function (SphygmoCor). Aortic Z_c and forward (P_f) and backward (P_b) wave amplitudes were calculated from central waveform using an aortic blood flow model based on higher-order Windkessel theory (ArcSolver), [Weber T et al, Hypertension EPub May 14, 2012].

Results: Patients with LV hypertrophy (LV mass >51 g/m^{2.7}) had a higher brachial systolic BP (SBP 153±18 vs 146±15 mmHg, p<0.001), central systolic BP (142±18 vs 133±16 mmHg, p<0.001), aortic Z_c (0.235±0.08 vs 0.211±0.06 AU, p<0.001), P_f (31.7±9 vs 28.6±7 mmHg, p<0.001), and P_b (19.8±7 vs 18.1±5 mmHg, p=0.02), while reflection magnitude (P_b/P_f) did not differ (0.62±0.10 vs 0.63±0.10, p>0.3). After controlling for age, sex, and mean arterial pressure as a measure of distending pressure, LV mass index maintained an independent association with Z_c (partial r=0.14, p=0.002), while the association of either P_b or P_f with LV mass became no longer significant. In a multiple linear regression model, Z_c independently predicted LV mass index ($\beta=0.116$, p=0.005) along with age, mean arterial pressure, and body mass index.

Conclusion: Aortic characteristic impedance has a significant, pressure-independent relationship with LV mass in human hypertension.

1.6

SPIRONOLACTONE REDUCES AORTIC STIFFNESS IN PEOPLE WITH A HYPERTENSIVE RESPONSE TO EXERCISE VIA THE BLOOD PRESSURE-DEPENDENT EFFECTS OF CANRENOATE

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Background: A hypertensive response to exercise (HRE) is associated with increased aortic stiffness. Spironolactone is thought to improve aortic stiffness via BP-independent (antifibrotic) effects, but the exact mechanisms are unknown. This study aimed to determine the underlying physiological actions of spironolactone in people with HRE.

Methods: 115 people with HRE (aged 54±9 years) were randomized to three months spironolactone (25mg/d) or placebo. Serum samples and physiological data including aortic stiffness (pulse wave velocity; PWV) and 24 hour ambulatory BP were recorded at baseline and three months. Liquid

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 (Δ IMT) is associated with WTS at baseline.

Methods: study population consisted of 749 healthy subjects at low-average Framingham risk (327 men, age = 45 ± 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 ($+18 \pm 58$ μ m, $p < 0.0001$) increased, whereas WTS (-0.27 ± 6.70 kPa, $p = 0.36$) remained unchanged. Δ 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 Δ IMT were male gender, age and WTS at baseline ($\beta \pm$ SE: 0.12 ± 0.04 , 0.17 ± 0.04 and 0.32 ± 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 ± 15 yrs, BMI: 29 ± 6 kg/m²) tonometric foot-to-foot carotid-femoral pulse wave velocity (cfPWV_{f-f}) 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_{DC}). 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_{DC}*), based on BP values measured at follow-up. In patients in whom diastolic blood pressure (DBP) was significantly reduced, cfPWV_{f-f} and (measured) cPWV_{DC} 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_{DC}* versus cfPWV_{f-f}: $r = 0.49$ ($p = 0.020$) and cPWV_{DC}* versus cPWV_{DC}: $r = 0.45$ ($p = 0.037$), while cfPWV_{f-f} versus cPWV_{DC}: $r = 0.26$ ($p = 0.22$).

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.