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P3.21: CONDUCTANCE AND CAPACITANCE EFFECTS OF ACUTE, ELECTRICAL, CAROTID BAROREFLEX STIMULATION

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Results: All patient presented with >80% stenosis in either of the internal carotid arteries. Mean YM was 108 (52-195) kPa. All five plaques varied in echogenicity classification. On histology, 2 plaques were 'probably or definitely' unstable and 2 were probably stable (Fig.1). There was better correlation between YM and histology finding compared to echogenicity.

Conclusion: This present insight into the role of novel ultrasonic based technique in providing further information in characterising carotid plaque properties which may be of value in identifying vulnerable plaques.

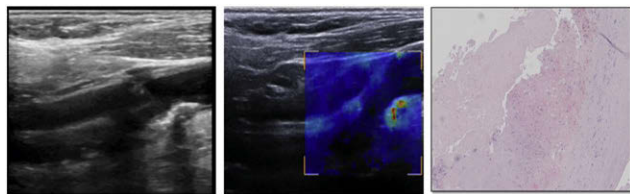


Figure 1 Patient with echogenic plaque on B-mode, YM of 66kpa and histology classification of definitely unstable.

P3.19

ALTERED WSS IN THE HUMAN AORTA WITH AGE – IMPLICATIONS FOR WALL REMODELLING AND LESIONS?

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Arteries are continuously affected by pulsating blood flow resulting in a wall shear stress (WSS) load. WSS has been related both to the remodeling process in the arterial walls as well as atherosclerosis. These processes are both related to ageing.

10 young (23.5±1.4 years, BMI 21.8±1.4) and 8 old (58.0±2.8 years, BMI 24.0±2.3) subjects were studied. Computational fluid dynamics (CFD) together with magnetic resonance imaging (MRI) measurements were used to investigate the WSS in the healthy thoracic aorta (TA). MRI images (geometry and flow) were obtained and segmented to fit the CFD simulations. Time averaged WSS (TAWSS) and oscillating shear index (OSI) were extracted. In young and old subjects, the diameter of the descending TA was 26±2.2 mm vs. 36±3.7 mm ($p < 0.001$), and cardiac output (CO) 6.75±1.04 L/min vs. 4.17±0.90 L/min ($p < 0.001$). In the whole TA, the TAWSS in the old was lower than in the young, while OSI only showed small differences. Fig 1a and b show reduced TAWSS with age in a cross-section of TA, and to some extent also in OSI.

Conclusions: WSS show distinct age-related changes with a major reduction in TAWSS, while OSI show only minor changes. This is associated with an increase in aortic diameter as well as decrease in CO. The distinct WSS-alterations could be a contributing factor both to the remodeling and atherosclerosis process over age.



Figure 1a cross-section location.

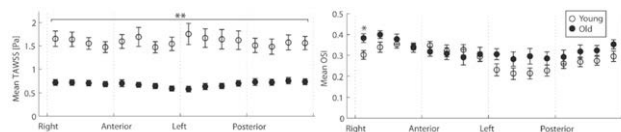


Figure 1b TAWSS and OSI distribution between the young and old subjects at a cross-section of the descending aorta (±SEM). Significance is indicated by * and ** ($p < 0.05$ and $p < 0.01$, respectively).

P3.20

ESTROGENS REGULATE ENDOTHELIAL NITRIC OXIDE PRODUCTION IN RATS ARTERIES DURING EARLY POSTNATAL PERIOD

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During maturation the vascular system undergoes structural and functional changes. Earlier we showed that endothelium of 1-2-week-old rats exerts an anticontractile effect due to tonic nitric oxide (NO) production which correlates with a higher eNOS expression level compared to adults. Estrogens are powerful regulators of eNOS expression and activity in arterial endothelium. This study tested the hypothesis that anticontractile effect of endothelium in young rats is associated with the influence of endogenous estrogens.

From the 2nd postnatal day male Wistar rats were daily treated with estrogen receptor blocker ICI182,780 (1 mg/kg/day, s.c.), age-matched control pups were treated with vehicle. On 10-12 postnatal days saphenous artery was isolated for measuring the levels of eNOS and aromatase mRNA expression (qRT-PCR) and contractions to methoxamine (alpha₁-adrenoceptor agonist) before and after eNOS inhibition (wire myograph, DMT A/S, Denmark). Serum estradiol concentration (ELISA) in young rats was 20% higher than in adults. mRNA expression levels of eNOS and aromatase, the key enzyme of estradiol synthesis, in pup arteries were much higher than in adults. Importantly, chronic ICI182,780 treatment reduced the impact of endothelium on methoxamine-induced contraction: eNOS inhibitor L-NNA had small effect in "ICI" group, but strongly potentiated the contraction in control. mRNA expression level of eNOS in ICI-treated group tended to be lower compared to control.

Our results suggest that estrogens (both blood-delivered and locally produced in the arterial wall) are important determinants of endothelial secretion in postnatal rats. Effects of estrogens lead to tonic NO production which weakens arteries responses to contractile influences.

P3.21

CONDUCTANCE AND CAPACITANCE EFFECTS OF ACUTE, ELECTRICAL, CAROTID BAROREFLEX STIMULATION

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Introduction: Chronic baroreflex activation is a therapy for resistant hypertension and has potential as a therapy in heart failure.

We hypothesized that acute baroreflex activation therapy (CVRx, Inc.) would increase both the capacity of the abdominal venous circulation (lowering "preload") and aortic conductance (reducing "afterload").

Methods: Six 20-kg mongrel dogs were anaesthetized and ventilated. Arterial blood pressure (BP) and diaphragmatic aortic and caval flow (ultrasonic) were measured. Venous capacity changes were evaluated using a modified Brooksby-Donald technique*. A CVRx electrode was affixed to the right carotid sinus.

BP and flow data were collected under control conditions and during device activation and drug infusions. Angiotensin II (ANG II) was infused to raise BP to hypertensive levels; the current from the device was then increased.

Results: Device activation decreased mean aortic BP 22.5±1.3 mmHg, decreased heart rate 14.7±3.4% and cardiac output 10.8±3.9%, increased aortic conductance 16.2±4.9%, and increased abdominal blood volume at a rate of 2.2±0.6 mL/kg/min (5-minute activations). ANG II infusion increased BP 40.3±3.4 mmHg and reduced venous capacitance at a rate of 1.1±0.5 mL/kg/min. Subsequent electrical stimulation restored BP to baseline while aortic conductance only returned to 82.3±3.3% of control. Venous capacitance increased at a rate of 3.4±0.7 mL/kg/min, reversing the ANG II effects.

Conclusions: Acute electrical activation of the carotid baroreflex increases arterial conductance, decreases BP, and increases venous capacitance.

Modulation of venous capacitance may be an important effect of baroreceptor activation in hypertension and heart failure.

* Wright CI *et al.*, *Can J Cardiol* 2004; 20:1127.

P3.22

EFFECT OF TISSUE TRANSGLUTAMINASE (TG2) ON CARDIAC AND VASCULAR FUNCTION IN YOUNG TG2 KNOCKOUT MICE

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Background: Structural changes of the arterial wall are associated with increased arterial stiffness and hypertension. Tissue transglutaminase (TG2), an enzyme ubiquitously expressed in the vasculature, forms stable crosslinks between extracellular matrix proteins, including collagen. Due to its role in small artery remodelling, calcification and atherosclerosis, TG2 has been implicated in cardiovascular disease. The aim of this study was to compare parameters of cardiac and vascular function between TG2 knockout mice and wild-type littermates.

Methods: Male TG2^{-/-} (n=4) and TG2^{+/+} (n=4) mice, aged 16 weeks, were anaesthetized with isoflurane. Aortic pressure was recorded with a 1.2F high fidelity sensor via the left carotid artery. Mean and pulse pressure and augmentation index were determined from the pressure signal; baroreflex sensitivity computed from directional changes of systolic pressure and interbeat interval (ECG), and aortic pulse transit time from the R wave to foot of the aortic pulse. Ventricular weight was expressed as percentage of total body weight.

Results: TG2^{-/-} mice showed significant differences only in relative ventricular weight compared to wild-type controls (Table).

Parameter	Wild-type	TG2 ^{-/-}
Heart rate (bpm)	619 ± 31	639 ± 26
Ventricle/body weight (%)	0.39 ± 0.016	0.44 ± 0.011*
Mean arterial pressure (mmHg)	76.5 ± 1.1	72.1 ± 4.2
Pulse pressure (mmHg)	30.4 ± 0.40	28.1 ± 1.1
Augmentation index (%)	20.0 ± 1.9	18.0 ± 1.8
Baroreflex sensitivity (ms/mmHg)	2.04 ± 0.72	2.17 ± 0.55
ECG - aortic pulse delay (ms)	15.43 ± 0.71	14.80 ± 1.9

*p<0.05

Conclusion: Although findings suggest a tendency for increased ventricular mass, TG2 does not influence other baseline cardiovascular parameters in young healthy mice. This is consistent with TG2 activity, which is modulated by Ca²⁺ and endothelial nitric oxide, being generally increased in inflammation and ageing. However, this study lays the ground work for future experiments in which inflammation or endothelial dysfunction will be induced, whereby TG2^{-/-} mice would be expected to be protected from associated increase in vascular dysfunction and stiffness.

P4 – Clinical Science

P4.01

PROXIMAL AND DISTAL AORTIC STIFFNESS AND CARDIAC FUNCTION IN YOUNG WOMEN

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Introduction: Diabetes and Hypertension affect cardiovascular structure and function. We investigated the relationship between large artery

structure (ascending aortic intima-medial thickness -aIMT), stiffness (ascending aortic distensibility-AAD & aortic pulse wave velocity-aPWV) and other cardiac structure and functional parameters by transthoracic echocardiogram (TTE) in a group of young pre-menopausal women without any cardiac disorder.

Patients and Methods: 83 women (age 35.8 years, 95% CI 34.7-36.8) underwent anthropometric, biochemical assessments, TTE and aPWV measurements. The aIMT was measured by 2-D mode by parasternal long axis view. AAD was computed using measurements of aortic root diameter in systole and diastole and aPWV by Doppler USS technique over descending aorta and thoraco-abdominal aorta between the origin of left subclavian artery and the bifurcation of the aorta.

Results: There was correlation between LV-Isovolumic relaxation time and AAD (r=0.336; p=0.03) but not with aPWV. There was no relation between LV posterior wall thickness and aIMT. After adjustment for age, body mass index, smoking history, day in menstrual cycle, systolic velocity time integral and total cholesterol only diastolic blood pressure was independently related to AAD (β: -0.18; 95% CI: -0.029 to -0.007; p=0.001) and to aPWV (β: 0.082; 0.027 to 0.138; p=0.004). Fasting plasma glucose influenced AAD (β: -0.212; -0.407 to -0.018; p=0.033) but not aPWV.

Conclusion: In young women, without overt diabetes, hypertension or pre-existing cardiac disease, proximal but not distal aortic stiffness was related to LV stiffness, in part influenced by BP, while glycaemia influenced only the proximal aortic stiffness independent of LV systolic function.

P4.02

ASSESSING VENTRICULAR-VASCULAR INTERACTIONS NON-INVASIVELY IN HEALTHY ADOLESCENTS

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Withdrawn by the author.

P4.03

ORAL LYCOPENE SUPPLEMENTATION IMPROVES ENDOTHELIAL FUNCTION IN PATIENTS WITH CARDIOVASCULAR DISEASE: A RANDOMISED CONTROLLED TRIAL

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Introduction: Lycopene is a potent antioxidant and carotenoid in the 'Mediterranean diet'. Plasma and adipose lycopene concentrations have previously been inversely correlated with cardiovascular disease (CVD) risk. We hypothesised that a standardised preparation of lycopene would improve endothelial function.

Methods: 36 healthy volunteers (HV) and 36 stable CVD patients on statins were randomised unequally (2:1) to either 7mg lycopene or placebo daily for 2 months (NCT01100385). Forearm blood flow responses to intra-arterial infusions of acetylcholine, (endothelium-dependent vasodilatation,EDV); sodium nitroprusside (endothelium-independent vasodilatation,EIDV); and N^G-monomethyl-L-arginine (measuring basal nitric oxide,NO) were measured using venous plethysmography.

Results: At baseline, both groups were similar in age, BP and hs-CRP but the CVD group had a lower LDL (2.4 ±0.6 vs. 3.6 ±0.9mmol/L, P<0.001). The CVD group had impaired EDV to ACh compared with HV (30% lower; 95%CI: -45, -10, P=0.008). Lycopene improved EDV in CVD patients by 53% (95%CI: +9, +93, P=0.03 vs. placebo) independent of changes in EIDV or basal NO. Lycopene did not change EIDV, EDV or basal NO in HV. Home blood pressure, LDL, HDL and hs-CRP levels were unchanged in both groups. A post-hoc analysis demonstrated that lycopene treatment improved EDV in CVD patients towards HV levels at baseline (3% lower; 95% CI: -30, +30, P=0.85), suggesting normalization of vascular function.

Conclusion: Lycopene supplementation improves endothelial function in CVD patients but not HV, and may require further investigation in larger outcome studies.