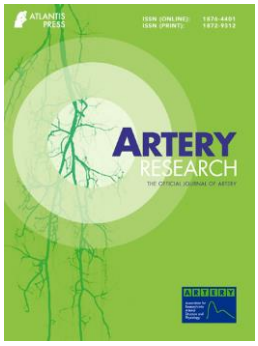

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9.3: FUNCTIONAL AORTIC CHANGES INDUCED BY A HIGH SALT DIET

Kathleen Connolly, Mark Butlin, Bart Spronck, Carmel McEniery, Alberto Avolio, Ian Wilkinson

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these WSR increase patterns may be associated with the subsequent brachial artery FMD response.

8.11
CARDIO-ANKLE VASCULAR INDEX AND CAROTID-FEMORAL PULSE WAVE VELOCITY ARE CLOSELY ASSOCIATED WITH CHRONOLOGICAL AGE

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Background: Vascular stiffening is part of the ageing process. However, it is not clear which vascular stiffness parameters are closely associated with chronological age.
Methods: Fifty-eight participants (38 men), age 69.57 ± 10.46 (mean ± SD, range = 47-90 years) who have had transient ischaemic attack or lacunar stroke within the last 2 weeks, had vascular stiffness parameters, brachial and central blood pressures measured. Cardio-ankle vascular index (CAVI) was measured with VaSera VS-1500N® (Fukuda Denshi, Japan); carotid-femoral pulse wave velocity (cfPWV) and carotid-radial pulse wave velocity (crPWV) were measured with Complior® (ALAM Medical, France); radial augmentation index (rAIx) and central blood pressure were measured with SphygmoCor® (AtCor, Australia).
Results: The mean and standard error of the mean for each parameter (mean ± SEM) was as follows: CAVI=9.77 ± 0.21, cfPWV = 10.61 ± 0.46 m/s, crPWV = 11.05 ± 0.30 m/s, rAIx = 31.34 ± 1.60 %, and central pulse pressure (cPP) = 50.22 ± 1.81 mmHg. In a bivariate analysis, CAVI ($r = 0.59$, $p<0.01$) and cfPWV ($r = 0.39$, $p<0.01$) were significantly associated with age, but rAIx ($r = 0.12$, $p = 0.371$) and crPWV ($r = 0.06$, $p=0.682$) were not. A multivariate regression analysis, performed with age as the dependent factor and CAVI, cfPWV, crPWV, cPP, and rAIx as independent parameters, showed that CAVI was the only significant parameter ($\beta = 0.49$, $p = 0.002$) associated with age.
Conclusion: CAVI and cfPWV are closely associated with chronological age, whereas crPWV and rAIx are less so. We suggest that the vascular parameter which best predicts biological age is CAVI, followed closely by cfPWV.

9.1
ULTRASOUND CHARACTERIZATION OF CARDIOVASCULAR ALTERATIONS IN YOUNG OB/OB MICE

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Obesity is associated with diabetes and an increased cardiovascular risk. Leptin-deficient mice (ob/ob) are used as model of metabolic disease: they are characterized by obesity and insulin-resistance. Aim of this work is to identify early cardiovascular alterations in young ob/ob mice using micro-ultrasound imaging.
Sixteen wild-type (wt) and eleven ob/ob male mice (8 wo,C57BL6) were studied. B-mode and PW-Doppler images were acquired with a micro-ultrasonographic system (Vevo2100) for assessing cardiovascular biomarkers. Left ventricular mass (LVmass), cardiac output (CO), ejection fraction (EF), stroke volume (SV), fractional shortening (FS) and E/A ratio were measured. Mean diameter (Dm_abd and Dm_car), relative distension (relD_abd and relD_car) and pulse wave velocity (PWVabd and PWVcar) were obtained for both abdominal aorta and common carotid. As regards renal microcirculation, renal resistivity and pulsatility index (RI and PI) were assessed. The ratio between grey-levels related to liver and kidney (HR_ratio) was used as index of hepatic steatosis grade.
ob/ob mice had higher glycemia levels (ob/ob:296±42mg/dl, wt:149±23mg/dl, $p<0.01$) and higher weight (ob/ob: 44.2g, wt: 31.1g, $p<0.01$). relD abd values were lower for ob/ob mice than for wt ones (ob/ob:18.6±4.1%, wt:23.8±3.3%, $p<0.01$) the ob/ob group presented also higher PWV (ob/ob:2.11±0.69m/s, wt:1.73±0.43m/s, $p<0.05$), RI (ob/ob:0.71±0.05, wt:0.64±0.06m/s, $p<0.01$) and PI (ob/ob:1.15±0.17, wt:0.97±0.12m/s, $p<0.01$) values. As concerns hepatic steatosis, there was a difference in HR ratio evaluations (ob/ob:1.27±0.26, wt:0.79±0.17, $p<0.01$).!
Young ob/ob mice have a reduced abdominal aorta distension capability and a higher value of stiffness for this vessel. Moreover, starting from young age, parameters related to renal microcirculation and hepatic fat accumulation are altered.

9.2
DELETION OF CHROMOSOME 9P21 NONCODING CARDIOVASCULAR RISK INTERVAL IN MICE INDUCES A PROTHROMBOTIC PHENOTYPE

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Background: SNPs on chromosome 9p21.3 risk locus have been associated with cardiovascular diseases. We have established a direct mechanistic link between 9p21 noncoding risk interval and susceptibility to aneurysm in a mouse model with a targeted deletion of the 9p21 noncoding cardiovascular disease risk interval.
The deficiency of transcripts encoded by this locus predisposes to a prothrombotic phenotype and arterial stiffening in this mouse model and in humans with 9p21 DNA variants.
Methods: Carotid blood flow following FeCl3 application was monitored via Doppler profiles. Results: The deletion of the orthologous 70-kb noncoding interval on mouse chromosome 4 (chr4Δ70kb/Δ70kb), synthetic to human chromosome 9p21, predisposes to arterial thrombosis. The time to occlusion in a FeCl3-induced carotid thrombosis model was significantly decreased by 30% in the absence of the locus and confirmed by a new model of physiological thrombosis. There was no difference between groups in blood pressure, carotid stiffness parameters (diameter and distensibility for a given level of arterial pressure) or in vascular structure. We explored the potential impact of the deletion locus on thrombin generation as well as on platelet aggregation and reactivity all were increased compared to controls. In 100 healthy carriers of the 9p21 risk T allele display an increased aortic arterial stiffness compared with carriers of the C allele.
Conclusion: These results establish a direct link between variants or deletion in the 9p21 non-coding risk interval and increased platelet reactivity and thrombin generation predisposing to thrombosis in mouse and increased arterial stiffness in aged population.
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9.3
FUNCTIONAL AORTIC CHANGES INDUCED BY A HIGH SALT DIET

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Objective: This study examines effects of high salt diet on arterial blood pressure and aortic function in rats.
Methods: Sprague-Dawley rats were fed either high salt content chow or normal chow from weaning. Weight, tail-cuff systolic blood pressure (SBP), water and food intake, and urine output were measured with age. At 16 weeks, rats were anaesthetised and thoracic and abdominal aortic blood pressure measured across a mean arterial pressure range of 60 to 150 mmHg, induced via intra-venous infusion of phenylephrine and sodium nitroprusside. Aortic pulse wave velocity (aPWV) and thoracic to abdominal aortic pulse pressure amplification (PPA) were calculated. Post-mortem weights of the left ventricle and kidneys were recorded. Statistical comparison between groups across the blood pressure range was by robust analysis of covariance.
Results: Rats on a high salt diet had lower weights ($p=0.04$) but similar body mass index. Food intake was similar whilst water intake was greater on a

high salt diet, with correspondingly greater urine output. Tail-cuff SBP was higher in rats on a high salt diet. There was no left ventricular hypertrophy ($p=0.16$) but greater kidney mass in high salt rats ($p=0.01$). High salt diet resulted in higher aPWV ($p<0.001$ at each 5 mmHg interval) and PPA ($p<0.001$ at each 5 mmHg interval).
Conclusions: High salt diet induced a moderate increase in arterial blood pressure, increased aortic stiffness, and higher PPA, indicating marked changes in transmission characteristics of the aorta including altered stiffness gradient and changed peripheral wave reflection characteristics.

9.4
EVOLUTION OF CARDIAC FUNCTION AND METABOLISM DURING AGING IN A MURINE ANIMAL MODEL OF OBESITY

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Purpose/Background/Objectives: Obesity is a well-known risk factor of cardiovascular diseases and a potentially modifiable determinant of arterial ageing. The objectives of this experimental study were to assess the effects of a long-term high fat diet (HFD) on metabolism, adipose tissues and phenotypes of cardiovascular aging.
Methods: Murine model chosen was C57BL/6J mice receiving during one year HFD or control diet (CD). Longitudinal follow-up of weight, systolic blood-pressure, heart rate and metabolic parameters was performed. An echocardiographic system was used to study cardiac function. Metabolism at the level of the adipose tissues was studied with FDG positron emission tomography (PET).
Results: After 12 months of diet the whole mice showed a positive correlation between plasma leptin level and left ventricular thickness and mass (both $p<0.05$).
As compared with the CD, the HFD was associated with metabolic disorders: higher body weight, hyperglycemia (both $p<0.01$) and increase in heart rate ($p<0.05$). Despite lack of modification of the systolic blood pressure, the HFD over 12 months increased left ventricular mass ($p<0.01$) and thickness of the inter-ventricular septum ($p<0.05$). Moreover, this parameter was positively correlated to leptin level ($p<0.05$). Finally, we observed in HFD mice a decrease of glucose metabolism in white fat after 6 months and 12 months and in brown fat only after 12 months (both $p<0.01$).
Conclusions: A long term HFD leads to metabolic disorders and to left ventricular morphological changes. The decrease of glucose metabolism observed in brown fat is compatible with an accelerate process of aging by the HFD.

9.5
COAGULATION CONTROL BY THE RHOA PATHWAY AND THE EXCHANGE FACTOR ARHGEF1

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Platelet activation by thrombin is an auto-amplification loop of thrombin generation, a major factor in the formation of atherosclerotic plaques. The small G protein RhoA, under the direct control of the exchange factor Arhgef1, modulates several cellular functions in inflammation. The objective was to study the RhoA pathway and its control by Arhgef1 in platelet aggregation and thrombin generation due to PAR receptor activation by thrombin.
We used a knockout mouse model for the exchange factor Arhgef1 (Arhgef1 -/-). In response to an agonist (collagen, ADP and thrombin), the expression of surface glycoproteins and the aggregation of washed platelets were not altered in the Arhgef1 -/- mice compared to Argef1 +/+ mice. In contrast, platelet activation studied by the secretion of granules a, exposure to phosphatidylserine and release of microparticles were decreased in the Arhgef1 -/- mice. Thrombin generation in whole platelet-rich blood was also reduced by 25%. These changes result in a lengthening of the time of occurrence of an occlusive thrombus in the carotid induced by $FeCl_3$.
In conclusion, the results confirm the involvement of the RhoA pathway in platelet activation and demonstrate an Arhgef1-dependent mechanism. The results in mice show a new auto-amplification mechanism of thrombin generation by platelets through PAR and membrane phospholipids. Redistribution of phospholipid linked rearrangements of the membrane complex induced by inflammation suggests that the RhoA pathway potentiates the deleterious effects of thrombin in atherothrombosis.
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9.6
VENTRICULAR VOLUME AND ARTERIAL FLOW DURING PRELOAD REDUCTION: AN MRI STUDY

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Lower body negative pressure (LBNP) has been used to assess the cardiovascular effect of preload reduction. We are the first to use MRI to investigate ventricular volumes and great vessel flow during LBNP.
13 volunteers (23-47years) underwent LBNP at 0, -5 and -20mmHg. We acquired contiguous short axis steady state free precession cine images (8mm slices) of both ventricles during relaxed expiratory breath hold, and flow images with free breathing phase contrast MR angiography of the ascending aorta (Ao) and main pulmonary trunk (MPA).
Analysis was performed using Argus software (Siemens Medical Solutions), statistical assessment by one-way ANOVA and Bonferroni post hoc tests with p-values adjusted for multiple comparisons.
At 5mmHg, no change in Ao flow, velocity or left ventricular (LV) volumes was seen. Diastolic blood pressure (DBP) increased ($p=0.04$). Right ventricular (RV) output ($p=0.01$) and MPA flow ($p=0.03$) was decreased.
At 20mmHg, Ao flow ($p<0.0001$) and velocity ($p=0.0005$) were decreased. Ao retrograde flow increased ($p=0.04$). LV stroke volume (SV, $p=0.0005$), ejection fraction (EF, $p=0.02$) and end diastolic volume (EDV, $p<0.0001$) decreased. DBP increased ($p=0.02$). MPA flow ($p<0.0001$) and velocity ($p<0.0001$) decreased, with no change in retrograde flow. RV EDV ($p<0.0001$) and ESV ($p=0.02$) reduced.
Our data implies (1) that at 5 mmHg LBNP there is an increased left to left shunt likely via the bronchial circulation to explain the different LV/Ao and RV/MPA response (2) different vasoconstrictive response in the systemic vs. pulmonary circulation to explain the differences in retrograde flow.