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

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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  $69.57 \pm 10.46$  (mean  $\pm$  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<sup>®</sup> (Fukuda Denshi, Japan); carotid-femoral pulse wave velocity (cfPWV) and carotid-radial pulse wave velocity (crPWV) were measured with Complior<sup>®</sup> (ALAM Medical, France); radial augmentation index (rAIx) and central blood pressure were measured with SphygmoCor<sup>®</sup> (AtCor, Australia).

**Results:** The mean and standard error of the mean for each parameter (mean  $\pm$  SEM) was as follows: CAVI =  $9.77 \pm 0.21$ , cfPWV =  $10.61 \pm 0.46$  m/s, crPWV =  $11.05 \pm 0.30$  m/s, rAIx =  $31.34 \pm 1.60$  %, and central pulse pressure (cPP) =  $50.22 \pm 1.81$  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 w, 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<sub>abd</sub> and Dm<sub>car</sub>), relative distension (relD<sub>abd</sub> and relD<sub>car</sub>) and pulse wave velocity (PWV<sub>abd</sub> and PWV<sub>car</sub>) 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<sub>ratio</sub>) was used as index of hepatic steatosis grade.

ob/ob mice had higher glycemia levels (ob/ob:  $296 \pm 42$  mg/dl, wt:  $149 \pm 23$  mg/dl,  $p < 0.01$ ) and higher weight (ob/ob: 44.2g, wt: 31.1g,  $p < 0.01$ ). relD<sub>abd</sub> values were lower for ob/ob mice than for wt ones (ob/ob:  $18.6 \pm 4.1$  %, wt:  $23.8 \pm 3.3$  %,  $p < 0.01$ ) the ob/ob group presented also higher PWV (ob/ob:  $2.11 \pm 0.69$  m/s, wt:  $1.73 \pm 0.43$  m/s,  $p < 0.05$ ), RI (ob/ob:  $0.71 \pm 0.05$ , wt:  $0.64 \pm 0.06$  m/s,  $p < 0.01$ ) and PI (ob/ob:  $1.15 \pm 0.17$ , wt:  $0.97 \pm 0.12$  m/s,  $p < 0.01$ ) values. As concerns hepatic steatosis, there was a difference in HR<sub>ratio</sub> evaluations (ob/ob:  $1.27 \pm 0.26$ , wt:  $0.79 \pm 0.17$ ,  $p < 0.01$ ).

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 pro-thrombotic phenotype and arterial stiffening in this mouse model and in humans with 9p21 DNA variants.

**Methods:** Carotid blood flow following FeCl<sub>3</sub> application was monitored via Doppler profiles. Results: The deletion of the orthologous 70-kb non-coding interval on mouse chromosome 4 (chr4Δ70kb/Δ70kb), synthetic to human chromosome 9p21, predisposes to arterial thrombosis. The time to occlusion in a FeCl<sub>3</sub>-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.

#### References

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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