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### **P3.15: LARGE EDDY SIMULATION OF AORTIC COARCTATION BEFORE AND AFTER SURGERY**

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enzyme, with anti-oxidative and anti-inflammatory properties, results in protection against atherogenesis. We investigated whether oxidative stress affects HO-1 induction differentially uremic or control conditions.

**Methods:** HUAECs were conditioned in 30% human serum conditions (pooled from 40 hemodialysis patients or 10 healthy volunteers) for 72h, followed by exposure to increasing concentrations of peroxynitrite (0.1-1mM) for 10 minutes in 100mM phosphatebuffer, pH 7.5. Additionally, HUAECs were incubated with 100 $\mu$ M Hemin during 6h. Cell viability was measured by MTT assay, 30 minutes after peroxynitrite exposure with or without hemin (50 $\mu$ M for 6h).

HO-1 expression was evaluated by RT-PCR, Western blot and ELISA.

**Results:** Equal cell viability was found when conditioned in uremic or control serum. Hemin treatment did not affect cell viability, but peroxynitrite treatment reduced cell viability by 23% and 43 % in control and uremic serum ( $P < 0.05$  vs. control). Hemin induced a 250-fold increase in HO-1 expression in both conditions. Consistent with mRNA induction, WB and ELISA confirm the induction of HO-1 by hemin in uremic and control conditions.

**Conclusion:** Although uremia is considered pro-oxidative, pro-inflammatory state, uremic serum per se does not affect cell viability. Oxidative stress however affects endothelial cell viability to a larger extent in uremic conditions compared to control. More work will be needed to determine whether the induction of HO-1 by Hemin is capable of abrogating oxidative-stress-induced processes, implicated in atherogenesis, in cells exposed to uremic toxins in the circulation.

### P3.12

#### A MONOCLONAL ANTIBODY TO THE ENDOGENOUS NA/K-ATPASE LIGAND, MARINOBUFAGENIN, REDUCES PROFIBROTIC GENE EXPRESSION AND REVERSES CARDIOVASCULAR FIBROSIS IN SALT-SENSITIVE HYPERTENSION

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Salt-sensitive hypertension is accompanied by elevated levels of an endogenous Na/K-ATPase inhibitor, marinobufagenin (MBG). Because MBG is implicated in cardiac fibrosis in experimental uremic cardiomyopathy (Hypertension 2007;49:215-24), we hypothesized that immunoneutralization of heightened levels of MBG in hypertensive Dahl salt-sensitive rats (DS) with monoclonal antibody may impact the profibrotic gene expression and cardiac remodeling.

We studied the following groups (n=6 each): (a) DS on a low salt (0.3% NaCl) diet (LS); (b) DS on a high salt (8% NaCl) diet for 7 weeks (HS); (c) DS on a high salt diet for 7 weeks, followed by monoclonal anti-MBG antibody treatment for 5 days (HSAB). Levels of MBG and of proteins implicated in pro-fibrotic signalling, and mRNA expression (microarray analysis) in left ventricles (LV) and aortae were assessed.

In HS vs. LS, BP increased by 74 mmHg ( $p < 0.01$ ), plasma MBG doubled ( $p < 0.05$ ), renal MBG excretion increased 6-fold ( $p < 0.01$ ), tissue weights increased (LV:  $2.37 \pm 0.05$  vs.  $1.62 \pm 0.04$  g/kg BW,  $p < 0.01$ ; aorta:  $4.44 \pm 0.17$  vs.  $3.01 \pm 0.06$  mg/mm<sup>2</sup>kg BW,  $p < 0.01$ ), and LV collagen rose 3.5-fold. In HSAB, BP was reduced by 35 mmHg ( $p < 0.01$ ), collagen-1 and LV and aortic weights were reduced ( $p < 0.01$ ) vs. HS group. In hypertensive DS there was a tissue-specific pattern of up-regulation of expression of genes, implicated in TGF $\beta$ -signaling (LV: TGF $\beta$ 1- $\beta$ 2, MAPK3, CTGF, SMADs, collagen-1; aorta: TGF $\beta$ 1- $\beta$ 3, PDGF, fibronectin, SNAIL1, PCOLCE, collagens), that was down-regulated following immunoneutralization of MBG.

Thus, immunoneutralization of MBG produces an anti-remodeling effect associated with down-regulation of genes implicated in TGF $\beta$ -induced fibrosis initiated by MBG in salt-sensitive hypertension.

### P3.13

#### ROLE OF THE SEMICARBAZIDE-SENSITIVE AMINE OXIDASE (SSAO) IN CELL DIFFERENTIATION: CONSEQUENCES IN ATHEROSCLEROSIS

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The « semicarbazide sensitive amine oxidase » (SSAO) transforms primary amines into aldehydes, ammonia and hydrogen peroxide and is widely expressed by vascular smooth muscle cells (SMC) from the arterial wall. SSAO

expression is increased during VSMC differentiation like in others cell types (adipocytes, chondrocytes). Disregulation of VSMC phenotype participates to the development of atherosclerosis lesion. To evaluate if the absence of SSAO could participate to the development of atherosclerosis, the laboratory established a double ApoE/SSAO knock out mice model (ApoE<sup>-/-</sup>SSAO<sup>-/-</sup>).

25 week-old ApoE<sup>-/-</sup>SSAO<sup>-/-</sup> mice presented a significant 50 % increase in plaque surface associated with an 80% decrease in a-actin expression in the media of aortic sinus from ApoE<sup>-/-</sup>SSAO<sup>-/-</sup> mice compared to ApoE<sup>-/-</sup> mice. We noticed a small T-cell infiltration in the media from ApoE<sup>-/-</sup>SSAO<sup>-/-</sup> mice whereas no T-cell infiltration was observed in the media from ApoE<sup>-/-</sup> mice. No difference was detected in monocytes/ macrophages infiltration in the plaque in aortic sinus from APOE<sup>-/-</sup>SSAO<sup>-/-</sup> mice and ApoE<sup>-/-</sup>. ApoE<sup>-/-</sup>SSAO<sup>-/-</sup> and ApoE<sup>-/-</sup> mice were transferred with labelled CD45.1 peripheral bone marrow cells from wild type mice. 5 day after PBMC injection, the number of labeled CD45.1 cells was increased in aorta, decreased in blood and unchanged in spleen from ApoE<sup>-/-</sup>SSAO<sup>-/-</sup> mice compared to ApoE<sup>-/-</sup> mice.

In conclusion, the absence of the SSAO increases the atherosclerosis in ApoE<sup>-/-</sup> mice. This result could be explained by a switch of VSMC to an inflammatory phenotype.

### P3.14

#### THE CONTRIBUTION OF RHO KINASE AND PROTEIN KINASE C IN CONTRACTION OF RAT RENAL SMALL ARTERIES: SMOOTH MUSCLE AND ENDOTHELIAL EFFECTS

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Noradrenaline released from sympathetic nerves by activating  $\alpha_1$ -adrenergic receptors causes renal artery contraction, in particular, through an inhibition of the myosin light chain phosphatase by Rho kinase (RhoK) and/or protein kinase C (PKC). In addition, both these kinases are expressed in endothelium and may influence the contraction through inhibition of endothelial NO-synthase (eNOS). The role of these kinases in contraction of renal arteries is poorly understood. Therefore, the goal of our study was to estimate the participation of RhoK and PKC in  $\alpha_1$ -adrenergic contraction of rat renal arteries and in regulation of eNOS activity.

Interlobar arteries (2-3-order branches of the renal artery) were dissected from the kidney of male Wistar rats and mounted in a wire myograph (DMT A/S, Denmark). The arteries were contracted for 10 min with methoxamine ( $\alpha_1$ -adrenoceptor agonist, 0.8-1.6 microM) up to 70-80% of the maximal response level. Preincubation with the RhoK inhibitor (Y27632, 3 microM) or PKC inhibitor (GF109203X, 1 microM) decreased the contractile response by 60-70%. However, in the presence of eNOS inhibitor L-NNA (100 microM) Y27632 or GF109203X reduced the contractile response to methoxamine by only 40-50%. Therefore, NOS inhibition attenuated the effects of RhoK and PKC inhibitors.

In conclusion, RhoK and PKC with almost equal potency strongly potentiate smooth muscle contraction in rat renal small arteries. Along with that, vasocontractile effects of these kinases in rat kidney are due to inhibition of endothelial NOS. Supported by RFBR (grant N10-04-01723-a).

### P3.15

#### LARGE EDDY SIMULATION OF AORTIC COARCTATION BEFORE AND AFTER SURGERY

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The blood flow through an aortic coarctation before and after corrective surgery was simulated using computational fluid dynamics (CFD) with a state-of-the-art scale-resolving turbulence model (Large eddy simulation, LES). In this manner, the transitional and turbulent effects in the pulsating blood flow could be accounted for. Aortic geometry and in-plane velocity profiles in the ascending and descending aorta were measured using MRI. The velocity profiles provided patient-specific flow boundary conditions for the fluid model. The simulation computed the turbulent kinetic energy (TKE) of the flow, which is a measure of the turbulent velocity fluctuations. High

levels of TKE are undesirable, as the increased fluctuations removes energy from the mean flow.

Surgery was performed to widen the coarctation and catheter measurements showed a decrease in pressure drop, which resulted in an increased flow rate. As a consequence of the increased flow, the local Reynolds number also increased. The results from the CFD-simulations confirmed the pressure drop, but also showed that for the post-surgery model TKE levels increased at peak systole in the immediate downstream region of the coarctation.

The relationship between pressure drop, flow rate, coarctation diameter and Reynolds number is non-linear, and if both the flow rate and coarctation diameter increase as an outcome of surgery, the local Reynolds number may also increase. This, in turn, can result in an elevation of TKE levels after surgery.



Figure 1 Volume rendering of TKE in pre- and post-surgery models

**P3.16**  
**EFFECTS OF SYMPATHETIC BLOCKADE ON PRESSURE DEPENDENT ABDOMINAL AORTIC STIFFNESS IN THE SPONTANEOUSLY HYPERTENSIVE RAT**

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**Background:** Increased sympathetic nerve activity (SNA) is associated with development of hypertension in spontaneously hypertensive rats (SHR). Elevated SNA increases arteriolar smooth muscle tone affecting peripheral resistance, however, the effect on large arteries is not well established. This study aimed to assess the effect of SNA on aortic stiffness in SHR using sympathetic blockade at different values of mean arterial pressure (MAP).

**Methods:** SHR of 10-15 weeks (n=15) were anaesthetized (urethane 1.3g/kg/ml) and ventilated. Aortic blood pressure and pulse wave velocity (PWV) were measured by two high fidelity catheter-tip pressure transducers in the abdominal aorta via the carotid and femoral arteries. Aortic diameters were measured using ultrasound (6.2 MHz) with vessel tracking software (ArtLab, Esaote). Aortic compliance was calculated from diameter and pressure signals. Measurements were taken at low (70 mmHg), intermediate (140 mmHg) and high (170 mmHg) values of basal MAP and following sympathetic blockade with hexamethonium (i.v 20mg/kg). Arterial pressure was varied by bolus injection of phenylephrine (i.v 30µg/kg).

**Results:** Increase in MAP was associated with increase in arterial stiffness indices. Following sympathetic blockade, there was a trend for reduction in compliance associated with a significant increase in pulse pressure at low MAP. There was no significant difference in parameters at other values of MAP.

MAP (mmHg)	Parameter	Control	Hex.	Difference %	P-value
70	C (ml/mmHg)	7.1 ± 1.6	6.2 ± 1.7	14.5	0.07
	PP (mmHg)	38.1 ± 5.6	42.3 ± 7.6	-9.9	0.03 *
	PWV (m/s)	2.9 ± 1.2	2.8 ± 1.1	3.6	0.14
140	C (ml/mmHg)	3.4 ± 1.0	3.3 ± 0.7	3.0	0.55
	PP (mmHg)	53.8 ± 4.8	54.8 ± 6.5	-1.8	0.43
	PWV (m/s)	5.3 ± 1.0	5.5 ± 1.0	-3.6	0.08
170	C (ml/mmHg)	2.0 ± 0.5	2.2 ± 0.4	-9.1	0.16
	PP (mmHg)	72.4 ± 10.9	71.7 ± 11.5	1.0	0.88
	PWV (m/s)	6.5 ± 1.3	7.0 ± 1.5	-7.14	0.13

C: compliance; PP: pulse pressure; PWV: pulse wave velocity; Hex: hexamethonium;

**Conclusions:** These data suggest that sympathetic blockade can potentiate a stiffening effect in the abdominal aorta at low MAP in the SHR. This may be due to reduction of smooth muscle tone transferring the load from elastin to collagen in the vessel wall.

**P3.17**  
**WALL TRACKING FOR THE ASSESSMENT OF AORTIC DISTENSIBILITY DURING A FOLLOW UP OF 49 DAYS IN ANGIOTENSIN II-INFUSED APOE-/- MICE**

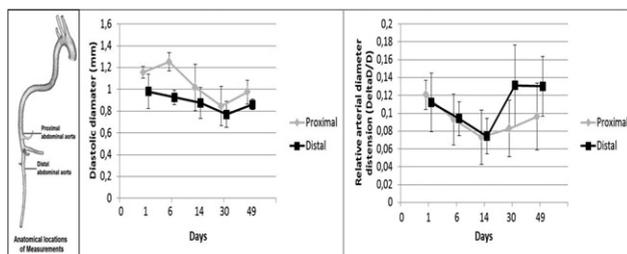
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**Introduction:** Ultrasound wall tracking allows assessing the distension of superficial arteries. While the technique is well established in humans, wall tracking is challenging in mice due to the smaller size of the arteries. The aim of this study was to assess the feasibility of sequential distension measurements on the aorta of an aortic aneurysm mouse model.

**Methods:** In-house bred male ApoE<sup>-/-</sup> mice were implanted an osmotic pump filled with Angiotensin II. Ultrasound data were obtained with a high-frequency ultrasound apparatus equipped with a linear array probe. All measurements were performed by a single operator. M-mode images of proximal and distal abdominal aorta were obtained in 5 animals on day 1, 6, 14, 30 and 49. Dedicated software was employed for wall tracking using stored demodulated Radio Frequency (RF) data. Resulting curves were processed to calculate the diastolic diameter and the relative (DeltaD/D) arterial diameter distension.

**Results:** Proximal abdominal aorta diastolic diameter presented higher values than distal abdominal aorta, as expected. However, diameter values in both locations decreased through time, reaching a minimum at day 30. DeltaD/D progressively decreased from baseline until day 14 in both locations, after which values increased to near baseline levels at day 49.

**Conclusion:** RF-based Vessel wall tracking of the abdominal aorta in an aneurysmatic mouse model is feasible. Our data suggest an initial narrowing and stiffening of the abdominal aorta up to day 14, followed by an increase in diameter and distensibility, a phenomenon that is possibly due to Angiotensin II-induced smooth muscle contraction.



**P3.18**  
**SHEAR WAVE ELASTOGRAPHY ASSESSMENT OF CAROTID ARTERY PLAQUE – HISTOLOGY FINDINGS**

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**Introduction:** Carotid atherosclerosis is a risk factor for ischaemic stroke. There is increasing interest in identifying and characterising high-risk unstable carotid plaques. Shear wave elastography (SWE) imaging is a new method of quantifying tissue stiffness with potential to provide additional information to help identify the unstable plaque and improve patient selection for surgical treatment. We evaluate this technique in assessing stiffness of carotid artery plaques by correlating histology findings to Young's modulus (YM) measured using SWE.

**Method:** 5 symptomatic patients undergoing carotid endarterectomy were recruited into the study. Prior to surgery, each patient underwent carotid ultrasound scan using SWE and B-mode. A longitudinal section of the carotid plaque was imaged. The YM of the plaques was compared to echogenicity and histological classification based on stability of the excised plaque.