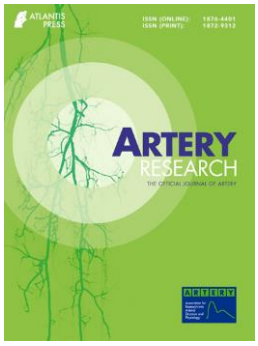

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6.5: ACUTE β-ADRENERGIC BLOCKADE INCREASES AORTIC WAVE REFLECTION IN YOUNG MEN AND WOMEN: DIFFERING MECHANISMS BETWEEN SEXES

D.P. Casey, T.B. Curry, M.J. Joyner, N. Charkoudian, J.N. Barnes, E.C. Hart

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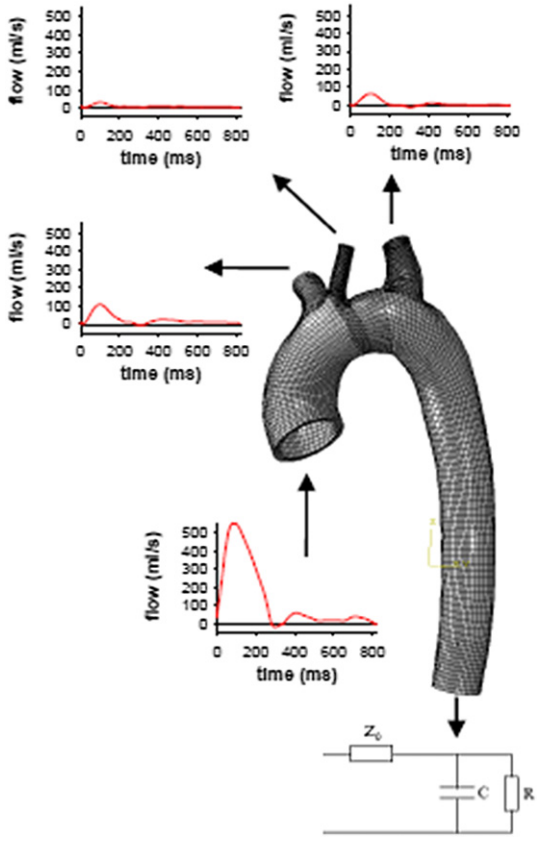

Figure 1 Patient-specific geometry and boundary conditions.

6.3
OXIDATIVE STRESS AND INFLAMMATION: IMPLICATION IN ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR AGING ON MURINE MODELS

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The aim of the study was to characterize cardiovascular aging with functional (Doppler) and molecular (RT-qPCR and immunohistochemistry quantifications) approaches using three murine models. Molecular studies on aorta (AO) and mesenteric arteries (MA) were used to explore the role of oxidative stress and inflammation. Time-induced aging model corresponded to 25 months-old C57Bl/6J mice feed with standard diet. Doppler exhibited a concentric left ventricle hypertrophy with a decreased aortic distensibility, and an increased aortic thickening. This model presented both a decreased Thioredoxin1 expression (AO and MA) and an increased NADPH oxidase (MA) expression. Inflammation markers were increased in MA (IL-1beta in MA and in AO (IL-6, TNF-alpha). Three months with High Fat and Protein Diet (HFPD) at 9 months induce a major hyperlipidemia. This model exhibited a dilated cardiopathy with both a decreased aortic distensibility and an increased aortic thickening. HFPD increased NADPH oxidase, IL1-beta and TNF-alpha expressions and decreased Thioredoxin1 expression (AO and MA). The mixed model corresponded to 25-months old C57Bl/6J mice feed for 3 months with HFPD. They presented a major cardiopathy with a decreased aortic distensibility, and exhibited both a major oxidative stress (increased NADPH oxidase and decreased Thioredoxin1 in AO and MA) and a major endothelial inflammation (increased IL-1beta, IL-6 and TNF-alpha in AO and MA). eNOS gene was not modify in any model. We conclude that NADPH oxidase and Thioredoxin1 seem to play a key role in the arterial aging process and might be interesting potential targets for therapeutics assays.

6.4
CARDIOTROPHIN-1 INDUCES STRUCTURAL AND MECHANICAL CHANGES IN AORTA

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Aims: Cardiotrophin-1 (CT-1), a cytokine belonging to the interleukin-6 family, exerts proliferative and secretory effects in vascular smooth muscle cells. We investigated the morphological, micromechanical and molecular vascular changes induced by chronic CT-1 administration in rats.
Methods: Recombinant rat CT-1 (20 μg/Kg, IP) or vehicle (n=10/group) was administrated to Wistar rats for six weeks. Vascular structure and function were determined with an echo-tracking device. Aortic extracellular matrix (ECM) protein production and attachments were quantified by immunohistochemistry, RT-PCR and Western blot. Acoustic wavespeed within the aorta was determined using a novel scanning acoustic microscopy (SAM) method at 1 GHz which enables tissues stiffness to be determined with a ~1 μm spatial resolution.
Results: In normotensive CT-1-treated rats, the incremental elastic modulus-circumferential wall stress curve was shifted leftward compared to vehicle, indicating increased arterial stiffness. Aortic media thickness was higher (40%) in CT-1-treated rats. Aortic collagen type I (80%), fibronectin (80%), metalloproteinases activities (40%), integrins (70%) and focal adhesion proteins (60%) were also increased in whereas elastin levels were similar to controls. Further, increased acoustic wavespeed in CT-1 rats (1694 ± 2 ms^{-1} compared to 1673 ± 2 ms^{-1}, $p<0.001$) was found in parallel with increases in collagen volume fraction (21 % as compared to 9 % in controls).
Conclusions: We demonstrate that CT-1 is a key player in arterial remodelling and stiffness by modulating aortic mechanical properties, media thickness, ECM production and attachments. Thus, CT-1 could be a new biotarget to reduce arterial stiffness and decrease ECM deposition in vascular diseases.

6.5
ACUTE β-ADRENERGIC BLOCKADE INCREASES AORTIC WAVE REFLECTION IN YOUNG MEN AND WOMEN: DIFFERING MECHANISMS BETWEEN SEXES

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Acute β-adrenergic blockade increases aortic wave reflection, however, the mechanisms remain unclear. Evidence suggests that β-adrenergic receptor sensitivity in the peripheral vasculature differs between sexes. Therefore, the goal of this study was to examine whether β-adrenergic blockade alters aortic wave reflection and forearm vasoconstrictor responsiveness to a similar extent in young men and women. In thirty-one subjects (16M/15F; 26±1 years) non-invasive aortic pressure waveforms were synthesized from high-fidelity radial pressure waveforms via applanation tonometry before and during systemic β-blockade (0.25 mg/kg bolus, followed by 0.004 mg/kg/min continuous infusion of propranolol). Forearm vasoconstrictor responses to exogenous intra-arterial norepinephrine (NE) were also assessed in a subset of subjects (13M/9F). Wave reflection characteristics are summarized in Table 1. β-blockade increased aortic augmentation index (AIx) and wave reflection amplitude (aortic augmented pressure (AG)) in both sexes. However, the increase in wave reflection tended to be greater ($P<0.05$ and $P=0.07$ for AG and AIx, respectively) in women following β-blockade. AIx adjusted for HR (AIx@75bpm) increased in women following β-blockade, whereas it was unchanged in men. Moreover, the change (Δ) in AIx was inversely associated to ΔHR only in men ($r=-0.54$, $P<0.05$). Finally, β-blockade caused an enhanced forearm vasoconstrictor response to exogenous NE in women (Figure 2). Our data suggest that: 1) aortic wave reflection is increased to a greater extent in women following systemic β-blockade; and 2) the mechanism for enhanced aortic wave reflection

appears to be mediated by a reduced HR in men, whereas less peripheral β-mediated vasodilation likely contributes in women.

Table 1 Hemodynamic variables before (control) and during systemic β-adrenergic blockade

	Men		Women	
	Control	β-Blockade	Control	β-Blockade
Heart Rate (bpm)	58 ± 2	50 ± 1†	62 ± 2	55 ± 2†
PSBP (mmHg)	123 ± 3	119 ± 3†	125 ± 3	121 ± 3†
PDBP (mmHg)	69 ± 3	70 ± 2	70 ± 2	70 ± 2
PPP (mmHg)	53 ± 2	48 ± 2†	55 ± 2	51 ± 1†
ASBP (mmHg)	102 ± 2	101 ± 2	107 ± 3	107 ± 3
ADBP (mmHg)	70 ± 2	71 ± 2	71 ± 2	71 ± 2
APP (mmHg)	32± 2	30 ± 0†	37 ± 2*	37 ± 2*
MAP (mmHg)	85 ± 2	85 ± 2	88 ± 2	88 ± 3
PPA	1.69 ± 0.03	1.62 ± 0.03†	1.54 ± 0.05*	1.44 ± 0.05*†
AIx (%)	-2 ± 3	2 ± 3†	10 ± 3*	17 ± 3*†
AIx@75bpm (%)	-10 ± 3	-10 ± 3	4 ± 3*	8 ± 3*†‡
AG (mmHg)	-0.5 ± 0.8	0.9 ± 0.8†	4.3 ± 1.5*	7.1 ± 1.6*†‡
Δtp (msec)	159 ± 4	163 ± 3	153 ± 4	153 ± 3
E_w (dyne· cm^2 · s)	-74 ± 152	233 ± 154†	864 ± 305*	1408 ± 345*†‡

PSBP, peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PPP, peripheral pulse pressure; ASBP, aortic systolic blood pressure; ADBP, aortic diastolic blood pressure; APP, aortic pulse pressure; MAP, mean arterial pressure; PPA, pulse pressure amplification, AIx, aortic augmentation index; AG, augmented pressure; Δtp, round trip time of pressure wave to the peripheral reflecting sites and back to heart; E_w, wasted left ventricular pressure energy. * $P < 0.05$ vs. men; †$P < 0.05$ vs. control; ‡$P < 0.05$ Magnitude of change vs. men

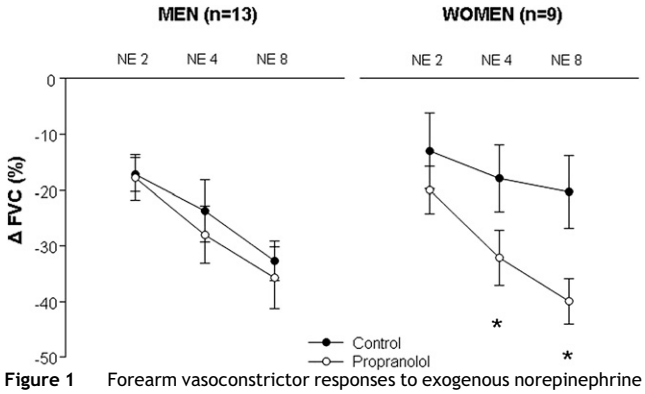

Figure 1 Forearm vasoconstrictor responses to exogenous norepinephrine (2, 4, and 8 ng/100 ml/min) in men and women before (control) and during systemic β-adrenergic blockade. * $P< 0.05$ vs. Control

6.6

RELATION BETWEEN BLOOD FLOW AND ARTERIOLAR MORPHOLOGY AND REDUCED VASODILATORY CAPACITY IN HYPERTENISIVE PATIENTS WITH INCREASED ARTERIOLAR WALL-TO-LUMEN RATIO IN THE HUMAN RETINAL CIRCULATION IN VIVO

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Objective: We hypothesized that blood flow and arteriolar morphological changes are related to each other in the human retinal vascular bed.
Methods: The study cohort comprised 141 non-diabetic untreated male patients with or without arterial hypertension but without evidence for cardiovascular disease. Retinal capillary blood flow (RCF) before and after exposure to flicker light and to infusion of nitric oxide (NO) synthase inhibitor N-monomethyl-L-arginine (L-NMMA), and parameters of retinal arteriolar morphology, e.g. wall-to-lumen ratio, were assessed non-invasively and *in vivo* by scanning laser Doppler flowmetry.
Results: Patients were grouped according to their median RCF into two groups. Patients with RCF above the median revealed lower wall-to-lumen ratio compared to patients with RCF equal or below the median (0.30±0.1 vs 0.34±0.1 (-), P adjusted = 0.023). In addition, RCF was inversely related to wall-to-lumen ratio independently of major cardiovascular risk factors (ß=-0.224, P=0.026). In parallel, the change of RCF to L-NMMA was greater in patients with RCF above the median compared to the counter group (-8.95±11 vs. 0.35±15 (%), P adjusted <0.001). The increase in RCF to flicker light, was inversely related to wall-to-lumen ratio in hypertensive but not in normotensive or all patients (r=-0.292, P=0.047, r=-0.035, P=0.746 and r=-0.126; P=0.144, respectively).
Conclusions: In the retinal circulation blood flow and arteriolar morphology are related to each other. Basal NO activity might impact on blood flow and arteriolar remodeling. In hypertensive, but not in normotensive patients, the vasodilatory capacity is inversely related to arteriolar wall-to-lumen ratio in the human retinal vascular bed.

Oral Session 7 Free Oral Communications In association with the 'European Society of Hypertension'

7.1

IMPACT OF 3D CULTURE OF MESENCHYMAL STEM CELLS TO REPAIR EXPANDING AAAS

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Abdominal aortic aneurysms (AAAs) are characterized by extracellular matrix degradation and mesenchymal cells rarefaction. In this context, the use of mesenchymal stem cells (MSCs) opens the way for the cell therapy to repair the damaged arterial wall. This study proposes to investigate a cellular therapy by using a 3D structure of MSCs encapsulated in a hyaluronic acid (HA) hydrogel. We show that the morphological remodeling is induced when the MSC is seeded in the hydrogel. The expression marker is not modified and the cell plasticity is better preserved in 3D culture in comparison with the 2D case. The comparison also shows that the ratio of apoptosis cell is reduced when physiological environment is mimicked by applying dynamical strain. Based on these results, the Xenograft model of AAA on the rat [1] is used to test the capability of the MSC to repair the aneurysm. Thus, after 7 days, the endovascular injection in rats tends to stabilize the diameter of AAAs. In summary, preliminary results indicate that (i) the proposed 3D HA hydrogel preserves most of MSC properties, (ii) the 3D culture may allow understanding better MSC stabilizing properties in AAAs, (iii) the investigation of the stresses in the artery wall would be necessary [2].
[1] E. Allaire, E. Guettier, C. Bruneval, P. Plissonnier, JB. Michel, *Cell-free arterial grafts: morphologic characteristics of aortic isografts, allografts, and xenografts in rats*, Journal of Vascular Surgery 19, 446-456, 1994.
[2] F. Mohand-Kaci, A. Eddhahak-Ouni, J. Dai, E. Allaire, M. Zidi, *Stochastic Modelling of Wall Stresses in Abdominal Aortic Aneurysms Treated by a Gene Therapy*, Computer Methods in Biomechanics and Biomedical Engineering, (doi:10.1080/10255842.2010.540759).

7.2

IN WHICH EXTENT GAMMA-GLUTAMYLTRANSFERASE CONTRIBUTES TO THE VASORELAXANT EFFECT OF S-NITROSOGLUTATHIONE?

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S-nitrosoglutathione (GSNO) exhibits higher stability than nitric oxide (•NO) and plays an important role in vasoreactivity as it serves as •NO storage and transport, and is a source for protein nitrosation. As gamma-glutamyltransferase (GGT) is involved in •NO release from GSNO, we investigated whether GGT influences the vasorelaxant effect of GSNO in the rat aorta.
We measured specific GGT activity in homogenates from thoracic aortic rings isolated from male adult Wistar rats (mean±S.E.M., 3 experiments,