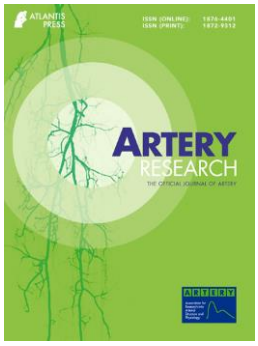

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7.2: IN WHICH EXTENT GAMMA-GLUTAMYLTRANSFERASE CONTRIBUTES TO THE VASORELAXANT EFFECT OF S-NITROSOGLUTATHIONE?

F. Dahboul, C. Perrin-Sarrado, K. Maguin Gate, A. Boudier, C. Gaucher-di Stasio, P. Liminana, I. Lartaud, A. Pompella, P. Leroy

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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

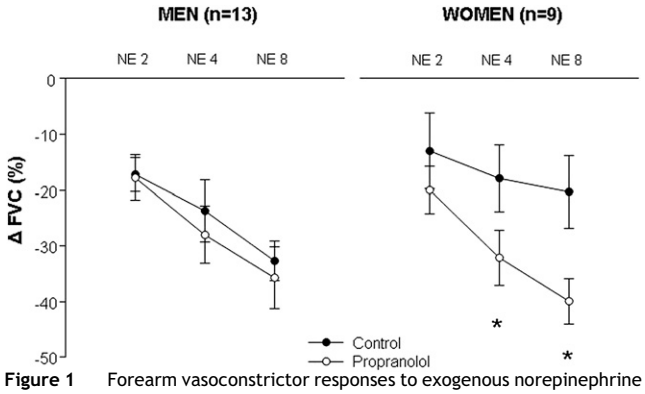

Figure 1 Forearm vasoconstrictor responses to exogenous norepinephrine (2, 4, and 8 ng/100 ml/min) in men and women before (control) and during systemic β-adrenergic blockade. * $P< 0.05$ vs. Control

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?

F. Dahboul [1], C. Perrin-Sarrado [1], K. Maguin Gate [1], A. Boudier [1], C. Gaucher-di Stasio [1], P. Liminana [1], I. Lartaud [1], A. Pompella [2], P. Leroy [1]
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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,

0.28±0.04 nmol/min/mg proteins) and confirmed that GGT activity was mainly localized in the endothelium (histochemical reaction). The GSNO consumption in aorta homogenates (absorbance decay at 334 nm, 2.4±0.2 nmol/min/mg proteins) decreased by 57±3 % in the presence of serine borate complex (SBC, 20 mM), a competitive inhibitor of GGT, and increased by 24 ± 4 % when adding an acceptor of gamma-glutamyl residue, glycylglycine (glygly, 20 mM). The resulting release of •NO (Griess method) and nitrosation of proteins (Saville-Griess assay), were either reduced or improved with SBC and glygly, respectively (fig 1). Then, concentration-response curves to GSNO were performed in aortic rings (6-8 per experiment) precontracted with phenylephrine (1 μM) (fig 2). Half maximal effective concentration (EC_{50} determined by an Hill model) for GSNO (0.26±0.07 μM) increased with SBC (1.35±0.11 μM, $p<0.05$) and decreased with glygly (0.054±0.01 μM, $p<0.05$).
Such involvement of GGT in the vasorelaxant effect of GSNO should be taken into consideration for further development of new therapeutics using GSNO analogues.

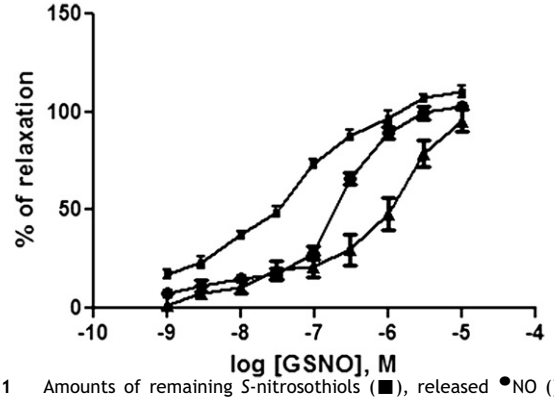

Fig. 1 Amounts of remaining S-nitrosothiols (■), released •NO () and nitrosated proteins (□) after incubation of 1 mM GSNO with aorta homogenates for 2 h at 37°C of, with and without SBC (20 mM) or glygly (20 mM). Data are means ± S.E.M. of 3 experiments. (* $p < 0.05$ *versus* GSNO alone)

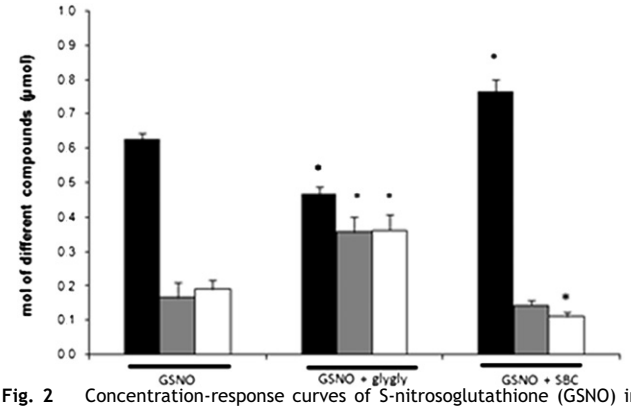

Fig. 2 Concentration-response curves of S-nitrosoglutathione (GSNO) in isolated rat aortic rings. The arteries were precontracted with 1 μM phenylephrine and concentrations (10^{-9}-10^{-5} M) of GSNO (●), GSNO + glygly (20 mM) (■) and GSNO + SBC (20 mM) () were added. Data are means ± S.E.M. of 6-8 experiments.

7.3
MICROCIRCULATION ABNORMALITIES AS RELATED TO ARTERIAL STIFFNESS AND CENTRAL BLOOD PRESSURE IN HYPERTENSIVE PATIENTS

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Background: The possible relationships between indicators of small resistance artery structure and of large artery distensibility have not yet been evaluated. Aim: to assess the relationship between carotido-femoral pulse wave velocity (CF-PWV), central blood pressure (cBP) and vascular alterations in small resistance arteries (media to lumen ratio, M:L) in patients with primary and secondary hypertension Patients and methods: In 65 patients (mean age 53±14 years, 31 F, 21 with diabetes mellitus type 2, 14 never treated) with essential (n= 32) and secondary (n=33) hypertension, pulse wave velocity was measured (Complior)and PW analysis was performed (Sphygmocor). In all patients small-resistance arteries were dissected from subcutaneous fat biopsies and mounted on an isometric myograph, for the measurement of the M:L. Results: Mean values of PWV and of M:L ratio were 11.4±2.6 m/s and 0.09±0.019, respectively. M:L ratio was significantly related to brachial systolic blood pressure (SBP) and pulse pressure (PP) ($r=0.40$ and 0.39, $p<0.001$, respectively) and to central SBP and PP ($r=0.44$ and 0.46, $p<0.001$, respectively). A positive correlation was observed between M:L and PWV ($r=0.43$, $p< 0.001$); this correlation remained statistically significant after adjustment for age and SBP (beta= 0.29, $p=0.03$). M:L ratio was also associated to augmentation pressure ($r=0.42$, $p< 0.001$); again this correlations remained statistically significant after adjustment for age, gender, mean BP and also for CF PWV. Conclusions: In hypertensive patients the presence of structural alterations of small resistance arteries may be associated with the increase in large arteries stiffness and, possibly contribute to an increase in central pressure by earlier wave reflections.

7.4
THE INFORMATION CONTAINED IN WAVE REFLECTION

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Wave reflection associates with cardiovascular events. However, it is less clear what information on arterial function, such as arterial stiffness and vascular resistance, can be derived. We therefore set out to find the relations between parameters obtained from wave shape analysis (Augmentation Index, Inflection and Shoulder points) and from wave separation analysis (Reflection Magnitude, and arrival time of the reflected wave) and aortic stiffness and taper.
Methods. We used a distributed model of the systemic arterial tree with properties as reported in earlier studies[1,2]. We changed vascular resistance, arterial stiffness and aortic taper.
Results. Peripheral Resistance has a negligible effect on wave reflection. Backward wave amplitude results, by equal amounts, from the distal aortic reflection (at length L) and from geometric taper and (other) aortic side branches. The wave reflected at the distal aorta runs with the same Pulse Wave Velocity (PWV) as the forward wave. The return time of the reflected wave, t_{return}, varies a factor two between small and strong taper. The t_{return} decreases 20% between aortic PWV's of 6 and 12 m/s, while 50% is predicted from $2L/t_{return}$. The timing of the shoulder and inflection points change with aortic stiffness but also less than predicted from 2L/PWV. The Augmentation Index and Reflection Magnitude ($P_{backward}/P_{forward}$) depend nonlinearly on stiffness; they increase with stiffness for low stiffness but not at high stiffness.
Characteristic impedance is needed for wave separation and therefore gives no independent information.
Conclusion. The data derived from wave form analysis and wave separation give poor information on arterial stiffness, no information on resistance and cannot be used to estimate these arterial parameters.
1. Westerhof et al.J Biomech 1969;2:121. 2. O'Rourke&Avolio Circ Res 1980;46: 363.

7.5
USING FINITE ELEMENT ANALYSIS TO MODEL ACOUSTIC RADIATION FORCE IMAGING (ARFI) OF CAROTID ARTERY PLAQUES

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The sudden rupture of carotid artery plaques can trigger an ischemic stroke event and eventually lead to death. Unfortunately, the identification of unstable plaques continues to elude clinicians. The use of Acoustic Radiation Force (ARF) to non-invasively provide a relative measure of tissue stiffness has shown promise for differentiating softer, lipid filled plaque regions believed to be more vulnerable than stiffer, calcified plaque regions[1].
A Finite Element Method (FEM) model to simulate the resultant displacements and associated stresses generated by ARF *in vivo* was implemented to