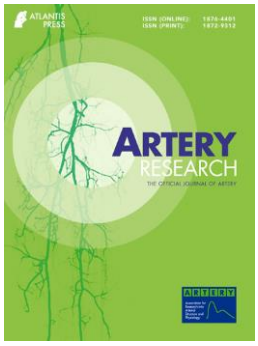

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P7.01: EFFECTS OF OMEGA 3 SUPPLEMENTATION ON ARTERIAL STIFFNESS IN RAT EXPERIMENTAL MENOPAUSE

P. Losurdo, E. Panizon, M. Jevnikar, L. Macaluso, B. Fabris, B. Toffoli, M. Bardelli, F. Fischetti, G. Biolo, M. Zanetti, S. Mazzucco, G. Gortan Capellari, R. Carretta

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significantly higher PWV values (11.5±2.7 and 11.4±3 m/sec respectively) than patients with normal heart geometry (10.2±2.6 m/sec) ($p \leq 0.001$ for both).
Conclusions: In EH patients arterial stiffness is associated with the degree of cardiac damage. This may reflect a common pathway leading to these alterations caused by hypertension in different but tightly related organs such as heart and arteries.

P6.06
SYSTEMIC ARTERIAL PROPERTIES DURING NORMAL PREGNANCIES IN HEALTHY WOMEN

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Purpose: During normal pregnancy (NP), the cardiovascular system adapts to the metabolic needs of mother and foetus with increased cardiac output (CO) and reduced vascular resistance. In NP blood pressure is not increased despite an increase of CO due to vasodilation of the resistance vessels. It is unknown whether this is also modulated by changes in the properties of the large arteries.
Methods: 65 (33±1 years) with NP were investigated at gestational weeks 14-16, 22-24, 36 and 6 months postpartum (PP). Aortic root pressure and flow were obtained by calibrated right subclavian artery pulse trace, and aortic annular Doppler flow recordings. Systemic arterial properties were described by total arterial compliance(C), arterial elastance (Ea), characteristic impedance (Z_0), and peripheral arterial resistance (R). Wave reflection was assessed as the ratio of the magnitude of the backward (Pb) to forward (Pf) pressure wave. Parameters were estimated by Fourier analysis of central aortic pressure and flow data and methods based on the 2-element windkessel model.
Results: (Table) During NP, CO increased due to increased heart rate and stroke volume, whereas, blood pressures were lower as compared to 6 months PP. R was significantly reduced accompanied by a marginally lowered Ea and $Z_{0,}$ whereas C was unchanged. The forward and backward pressure wave-amplitudes were significantly reduced, and reflection magnitude trended lower in mid to late pregnancy.
Conclusions: During NP profound alterations of systemic hemodynamics occur, with increased cardiac output and reduced blood pressures, where the latter is related mainly to reduction in peripheral arterial resistance.

	14-16 weeks	22-24 weeks	36 weeks	6 months PP	ANOVA P
Mean arterial pressure (mmHg)	82.8 ± 6.6	80.0 ± 6.2#	84.8 ± 7.1#¤	88.0 ± 7.3¤	<0.001
Heart rate (min^{-1})	71 ± 7	74 ± 8#	77 ± 10#¤	66 ± 7 #¤§	<0.001
Cardiac output (l min^{-1})	6.1 ± 1.1	6.1 ± 1.1	5.8 ± 1.0	4.9 ± 0.9 #¤§	<0.001
R (mmHg ml^{-1} s^{-1})	0.85 ± 0.18	0.81 ± 0.16	0.92 ± 0.23¤	1.10 ± 0.29#¤§	<0.001
Z_0 (10^3–mmHg ml^{-1} s^{-1})	43 ± 18	51 ± 36	45 ± 23	55 ± 21	0.168
C WK (ml $mmHg^{-1}$)	1.45 ± 0.33	1.56 ± 0.45	1.55 ± 0.46	1.40 ± 0.45	0.220
C PPM (ml $mmHg^{-1}$)	1.25 ± 0.26	1.23 ± 0.28	1.22 ± 0.33	1.14 ± 0.30	0.454
Ea (mmHg ml^{-1})	1.0 ± 0.25	1.02 ± 0.24	1.19 ± 0.28¤	1.27 ± 0.28#¤	<0.001
Amplitude Forward Wave (Pf; mmHg)	31 ± 6	30 ± 9	28 ± 5#	30 ± 6	0.013
Amplitude Backward Wave (Pb; mmHg)	20 ± 3	17 ± 4#	17 ± 4#	19 ± 4§	<0.001
Reflection magnitude (Pb/Pf)	0.64 ± 0.13	0.59 ± 0.15	0.61 ± 0.13	0.64 ± 0.13	0.051

Mean ± SD. p< 0.05 vs #14-16 w, ¤22-24 w, §36 w. WK = C obtained using windkessel model fit; PPM= pulse pressure method.

P6.07
AORTIC STIFFNESS IS AN INDEPENDENT PREDICTOR OF NEW ONSET ATRIAL FIBRILLATION IN CHRONIC HEART FAILURE PATIENTS WITH REDUCED SYSTOLIC FUNCTION

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Background: Atrial fibrillation (AF) is the commonest supraventricular arrhythmia in chronic heart failure (CHF) with impaired left ventricular (LV) systolic function, The causes of its high incidence and prevalence in CHF are only partially understood.
Aim: To analyze the hemodynamic determinants of incident atrial fibrillation in CHF patients. Particulary, whether indexes of arterial stiffness might identify patients at risk for new onset AF.
Methods: 77 patients (mean age 62.8±9.3 years, ejection fraction 34.5±8.3%, male 80%) were enrolled. All patients underwent a complete echocardiographic-Doppler evaluation. Aortic-pulse wave velocity (PWV) was determined by Doppler flow recordings as previously reported. Effective arterial elastance (Ea) was estimated as end-systolic pressure/stroke volume (SV). Total arterial compliance (SAC) was calculated as SV/PP.
Results: 15 (19.5%) patients developed AF during the follow up. There were no differences in age, SBP, DBP, PP, LV-EF, left atrial volume, plasma neurohormones and procollagens. Those with AF had higher aortic-PWV (7.0±2.5 vs 5.3±1.9 m/sec, p= 0.004), higher Ea (1.68±0.46 vs 1.35±0.47 mmHg/mL, p=0.03), lower SAC (1.57±0.55 vs 1.96±0.53 mL/mmHg, p=0.02), higher time difference between pulmonary vein Ar-wave and mitral A-wave duration (PV-Ar-A) (43.5±44.2 vs 10±34.7 ms, p=0.02) and mitral E-wave velocity (0.76±0.23 vs 0.59±0.24 m/s, p=0.02). In bivariate logistic regression models aortic-PWV predicted always independently incident AF:

Variables	OR	95% CI	p-value
Aortic-PWV	1.4	1.07-1.94	0.01
SAC	0.3	0.07-0.96	0.04
Aortic-PWV	1.5	1.09-1.97	0.01
Ea	2.9	0.95-8.9	0.06
Aortic-PWV	1.9	1.2-3.0	0.003
PV-Ar-A	1.04	1.0-1.07	0.01

Conclusion: Aortic stiffness independently predicts incident AF in CHF with impaired LV-systolic function.

Experimental Studies
P7.01
EFFECTS OF OMEGA 3 SUPPLEMENTATION ON ARTERIAL STIFFNESS IN RAT EXPERIMENTAL MENOPAUSE

P. Losurdo, E. Panizon, M. Jevnikar, L. Macaluso, B. Fabris, B. Toffoli, M. Bardelli, F. Fischetti, G. Biolo, M. Zanetti, S. Mazzucco, G. Gortan Capellari, R. Carretta
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Aim: To investigate the effects of omega-3 (Ω3) dietary supplementation on large artery mechanics and vascular oxidative stress (VOS), in a rat model of surgical menopause.
Materials and methods: Thirty, 6-months-old, Wistar-Kyoto rats were equally divided into 3 groups: a) control: sham surgery - normal diet (CTRL)-, b) ovariectomy, - normal diet (OVX) -and c) ovariectomy, + Ω3 supplementation (0,8g/Kg/day - daily gavages administration-) (OVX+Ω3). Two months after surgery, carotid-femoral Pulse Wave Velocity (c-f PWV) and arterial pressure were directly measured, by aortic and femoral catheter. VOS was assessed by superoxide anion generation, in aorta rings, (SOD-inhibitable cytochrome C reduction assay). Erythrocytes membrane Ω3 index was measured by gas-chromatography.

Results: The results are shown in the table:

Variable	CTRL	P-value	OVX	P-value	OVX+Ω3
Final body weight (gr)	211±3,85	0,005	246,4±11,7	< 0,0001vsCTRL	263,3±7,3
c-fPWV cm/sec	378,9±7,2	<,0001	560,8±12,1	< 0,0001	363,3±5,9
MeanBP mmHg	108,8±4,8	0,002	129,8±2,6	0,003	109,3±2,7
Superoxide nmol/min/mm^2	97,4±8,3	0,01	142,3±14,6	0,04	105,0±9,8
SystolicBP mmHg	133,1±6,1	0,07	153,3±12,9	0,11	135,9±4,1
DiastolicBP mmHg	96,7±4,6	0,09	109,1±6,9	0,1	97,2±2,6
Ω3 index, percent	3,2±0,1	0,01	2,5±0,08	< 0,0001< 0,0001vsCTRL	5,2±0,2

Conclusions: Ω3 supplementation reduces arterial BP and restores mechanical arterial properties in a post menopause experimental model, likely by restoring NO availability.

P7.02
EFFECT OF CAPTOPRIL AND TELMISARTAN ON ANTI-CONTRACTILE PROPERTY OF PERIVASCULAR ADIPOSE TISSUE LOST AFTER HYPOXIA IN RAT MESENTERIC SMALL RESISTANCE ARTERIES

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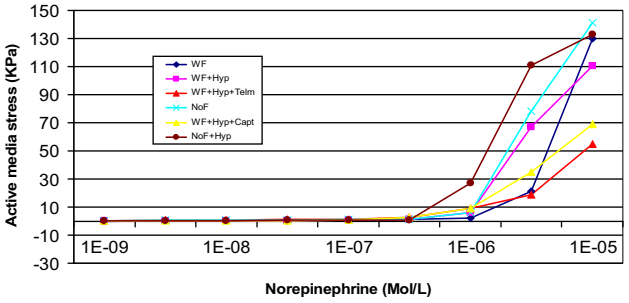
It has been previously demonstrated that inflammation in adipose tissue may be implicated in vascular dysfunction. Adipocytes secrete adiponectin, a physiological modulator of local vascular tone through an increased nitric oxide bioavailability. This capacity is lost in obesity by the development of adipocyte hypertrophy, leading to hypoxia, inflammation, and oxidative stress.
Aim: of the study was to investigate the feasibility a pharmacological modulation of the concerned effect, during hypoxia, in Wistar-Kyoto normotensive rats(WKY).
Materials and Methods: we investigated 25 WKY of 12 weeks of age. Mesenteric small resistance arteries were dissected and mounted on a wire myograph, according to Mulvany-Halpern technique(internal diameter about 200 μm). A concentration-response to norepinephrine(NE, from 10^{-9}to10^{-5}Mol/l)was evaluated in the following conditions:1)in vessels with perivascular fat tissue(WF),2)in vessels without perivascular fat tissue(NoF);3)in WF vessels under hypoxic condition(WF+Hyp);4)in NoF vessels under hypoxic condition(NoF+Hyp);5)in WF+Hyp vessels incubated with telmisartan10^{-2}Mol/l (WF+Hyp+Telm)or captopril10^{-2}Mol/l for 3hour(WF+Hyp+Capt).
Results: Are summarized in the figure(active media stress: KPa, mean of two vessels for each rat). A significantly greater reactivity to NE was observed in NoF vessels compared with WF vessels(ANOVAp=0.003between curves). This increased reactivity is similar to that observed in WF+Hyp(ANOVAp= NS between, NoF and WF+Hyp). Captopril and Telmisartan were able to prevent the effect of hypoxia(ANOVA $p<0.05$ between WF+Hyp and WF+Hyp+Capt or Telm).
In conclusion the ACE inihibitor captopril and the angiotensin-receptor blocker telmisartan seem to be able to restore the anti-contractile effects of perivascular fat tissue lost after hypoxia, possibly through an inihibition of angiotensin II effects.



P7.03
DIFFERENT EFFECT OF NEURONAL AND ENDOTHELIAL NOS INHIBITION ON HEART, CORONARY AND CAROTID ARTERY OF WISTAR RATS

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Long-term decrease of nitric oxide (NO) production evokes alterations in function and structure of cardiovascular system. We demonstrate the long-term effect of NO synthases inhibition with two different inhibitors on blood pressure (BP), heart and structure of coronary and carotid arteries. Four groups of ten weeks old Wistar rats were used: 1) control rats and rats receiving 2) N^G-nitro-L-arginine methylester (L-NAME) (50 mg/kg/day in tap water), 3) 7-nitroindazole (7NI) (10 mg/kg/day in tap water), 4) the same doses of L-NAME (in tap water) and 7NI (in pellet diet). The experiment lasted 6 weeks. BP was measured by the plethysmographic method weekly. At the end of the experiment the animals were perfusion with a glutaraldehyde fixative (120 mmHg) and heart, coronary and carotid artery were excised and processed for electron microscopy.

	Wistar	L-NAME	7NI	L-NAME+7NI
BP (mmHg)	112±2.20	164±2.10*	118±1,90^{+}	131±5,12$^{*+\#}$
H/B (mg/g)	3,08±0,14	3,41±0,13*	2,64±0,10^{*+}	3,07±0,12$^{+\#}$
Coronary a. CSA (μm^2)	8860±800	18280±1320*	6780±610^{*+}	14250±2290 $^{*+\#}$
Carotid a. CSA (μm^2)	69190±2460	109780±4040*	54290±2200^{*+}	88950±4340$^{*+\#}$

Blood pressure (BP), heart/body weight (H/B), cross sectional area — intima +media (CSA). *P<0.01 vs. Wistar, $^{+}$P<0.01 vs. L-NAME, $^{\#}$P<0.01 vs. 7NI
The study revealed, for the first time, that long-term inhibition of nNOS with 7NI, contrary to eNOS inhibition with nonspecific inhibitor L-NAME, evoked pressure independent cardiac hypotrophy and hypotrophy of the vessel wall. The data suggested that long-term nNOS inhibition likely iniciates a different chain of events leading to alterations in cardiovacular system then those after eNOS inhibition.
The study was supported by VEGA grant 2/0111/10, 2/0019/09.

P7.04
EVALUATION OF AORTIC STIFFENING IN HYPERTENSIVE RAT MODELS IN VIVO VIA ECHOTRACKING: PULSATILE DISTENSION WAVEFORM ANALYSIS

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Objectives: Large artery stiffening, a risk factor in cardiovascular diseases, can be evaluated in human and rats by pulse wave velocity and echotracking, but controversies remain regarding the roles of blood pressure (BP) and vascular wall properties. We studied these points with the echotracking device ArtLab in the hypertensive rat (SHR) treated with L-NAME (SHRLN) to reduce nitric oxide levels.
Methods: In anaesthetized normotensive rats (WKY), SHR and SHRLN 20 weeks old, aortic BP is recorded via a catheter and diameter via the ArtLab ultrasound probe, in a motion mode to detect pulsatile displacement of aortic walls (distension). Data are analysed via a Matlab software.
Results: Compliance and distensibility are decreased in SHRLN (<SHR<WKY) and stiffness index increased. From distension-pressure loop curves, ascending, descending slopes and isobaric ascending slope at 200 mmHg are reduced in SHRLN<SHR<WKY. If we plot pulsatile time-waveform curves of pulse pressure (PP) and distension in % (Figure), maximal values and waves kinetics are altered. We therefore calculate a distensibility index as area under the curves of distension/PP. Diltiazem i.v. in SHRLN decreases systolic BP and PP to values similar to those in WKY; compliance, distensibility and stiffness reach only the values of SHR. Isobaric compliance at 160 mmHg is < than in WKY and distension remains lower than in SHR.
Conclusions: This study shows that 1) the ArtLab device analyses accurately compliance and stiffness indexes in animal models and 2) adding an analysis of aortic distension pulse waveform allows additional evaluation of BP-independent vascular wall stiffening.