

**Table 1**

	WKY	ZSF1 Ln	ZSF1 Ob	ZSF1 OB WD
<b>Histology</b>				
Media thickness ( $\mu\text{m}$ )	60 $\pm$ 3.6	63 $\pm$ 3.2	62 $\pm$ 4	64 $\pm$ 3.1
Lumen radius ( $\mu\text{m}$ )	498 $\pm$ 8.8	562 $\pm$ 11.0*	593 $\pm$ 23.0*	584 $\pm$ 11.4*
Ratio media thickness/lumen radius	0.12 $\pm$ 0.009	0.12 $\pm$ 0.005	0.11 $\pm$ 0.006	0.11 $\pm$ 0.004
Medial cross sectional area ( $\text{mm}^2$ )	0.184 $\pm$ 0.015	0.207 $\pm$ 0.014	0.22 $\pm$ 0.028	0.20 $\pm$ 0.010
<b>Passive properties</b>				
AT at $l_{max}$ ( $\text{mN.mm}^{-1}$ )	5.3 $\pm$ 0.4	10.0 $\pm$ 0.4*	10.4 $\pm$ 0.7*	9.9 $\pm$ 1.2*
$\beta$ ( $\epsilon^{-1}$ )	0.94 $\pm$ 0.03	1.18 $\pm$ 0.07*	1.38 $\pm$ 0.08*	1.79 $\pm$ 0.06*
<b>Reactivity</b>				
Phe <sub>max</sub> ( $\text{mN mm}^{-1}$ )	7.0 $\pm$ 0.2	10.0 $\pm$ 0.4*	12.0 $\pm$ 0.4*	10.0 $\pm$ 0.2*
Phe <sub>EC50</sub> (nM)	220 $\pm$ 44	28 $\pm$ 7.6*	21 $\pm$ 6.2*	21 $\pm$ 5.1*
Ach relaxation <sub>max</sub> (% Phe contraction)	84 $\pm$ 3	56 $\pm$ 4*	43 $\pm$ 2*	38 $\pm$ 4*
Ach relaxation <sub>EC50</sub> (nM)	74 $\pm$ 2.4	122 $\pm$ 34.4*	226 $\pm$ 47.7*	449 $\pm$ 58.7*
SNP relaxation <sub>max</sub> (% Phe contraction)	89 $\pm$ 3.8	79 $\pm$ 1.44	54 $\pm$ 4.37*	55 $\pm$ 2.97*
SNP relaxation <sub>EC50</sub> (nM)	40 $\pm$ 8.3	74 $\pm$ 4.4*	159 $\pm$ 14.9*	244 $\pm$ 13.3*

AT: active tension;  $l_{max}$ : length at which maximum tension was achieved; Phe: phenylephrine; Ach: acetyl-choline; SNP: sodium nitroprusside.

During evaluation of elastic stiffness constant ( $\beta$ ) of passive tension relationships, strain ( $\epsilon$ ) was defined as proportional increase in lenght from slack length. Values are mean  $\pm$  SEM, n = 10, each group. \*p < 0.05 vs WKY; p < 0.05 vs ZSF1 LN; p < 0.05 vs ZSF1 Ob with one-way ANOVA.

ZSF1 obese fed with high fat diet (n = 10 for each group). Two 1.5 mm-long rings were isolated and mounted in a tissue bath system. Then, a strain-passive tension curve was constructed by gradually stretching the vessels in 20% $L_0$  uniaxial displacement increments. Simultaneously, a strain-active tension curve was determined by stimulating the vessels with KCl after each displacement increment. The strain-passive tension curve was fitted using the exponential equation  $f = y_0 + A \cdot \exp(B \cdot x)$ , and the "B" value was taken as a strain independent stiffness index. In separate experiments, a concentration-response curve to phenylephrine was then obtained (10<sup>-9</sup> to 10<sup>-5</sup>). After contracting again with phenylephrine (10<sup>-5</sup>), the vessels were challenged with increasing concentrations of either acetylcholine or sodium nitroprusside (10<sup>-9</sup> to 10<sup>-4</sup>). After completion of mechanical or functional evaluation, the aortic rings were immersed in 10% formalin. Transverse 4- $\mu\text{m}$ -thick sections of paraffin-embedded aorta were stained with H E for vascular measurements. For the sake of simplicity, results regarding histological analysis, mechanical testing and vascular reactivity are presented in detail in the attached figure. In conclusion, animals with metabolic syndrome show an increased aortic stiffness accompanied by impaired relaxation, the latter being attributed to both endothelial dysfunction and also decreased NO sensitivity. At the same time we found histological changes compatible with eutrophic outward remodeling. These results support a possible connection between endothelial dysfunction and large vessel passive properties changes in metabolic syndrome (table 1).

#### CO 63. A NEUREGULINA-1 ATENUA A DISFUNÇÃO ENDOTELIAL NA HIPERTENSÃO ARTERIAL PULMONAR

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**Introdução:** A neuregulina (NRG)-1 pertence à família do factor de crescimento epidérmico e tem importantes ações na manutenção da integridade estrutural e funcional do coração. No entanto, até à

data não existem estudos sobre os efeitos vasculares pulmonares da NRG-1. Assim, neste trabalho foi nosso objectivo determinar os efeitos do tratamento crónico com NRG-1 na disfunção endotelial vascular pulmonar, utilizando um modelo animal de hipertensão arterial pulmonar (HAP).

**Material e métodos:** Ratos Wistar (180-200 g) receberam aleatoriamente monocrotalina (MCT, 60 mg/Kg, sc) ou veículo. Após 14 dias, estes animais foram tratados aleatoriamente com NRG-1 (40  $\mu\text{g}/\text{Kg}/\text{dia}$ , ip) ou com igual volume de veículo. O estudo crónico resultou em 3 grupos: controlo (CTRL, n = 8); MCT (n = 8) e MCT+NRG (n = 5). Decorridos 21-24 dias após a administração de MCT, procedeu-se à excisão do pulmão e isolamento e montagem de anéis arteriais pulmonares num miógrafo. A função endotelial foi determinada com o uso de curvas concentração-resposta para a acetilcolina. No final do protocolo, os anéis foram guardados numa solução fixadora de formol tamponado (10%) para posterior análise histológica. Apenas os resultados significativos (média  $\pm$  EPM; p < 0,05) são apresentados.

**Resultados:** Os animais do grupo MCT desenvolveram HAP associada a disfunção endotelial, comprovada pelo relaxamento diminuído em resposta à acetilcolina, quando comparado com os animais do grupo CTRL (MCT versus CTRL: 35,41  $\pm$  4,02% versus 86,27  $\pm$  1,85%). Por outro lado, os animais tratados (MCT+NRG) mostraram uma melhoria significativa da função endotelial (48,31  $\pm$  5,69%). A análise histológica revelou a ocorrência de remodelagem vascular nos anéis arteriais dos animais do grupo MCT, quando comparados com o grupo CTRL, avaliada pela espessura da túnica média (MCT versus CTRL: 53,24  $\pm$  1,84 mm versus 31,33  $\pm$  0,83 mm), área da túnica média (MCT versus CTRL: 104,50  $\pm$  7,48  $\text{mm}^2$  versus 67,85  $\pm$  3,93  $\text{mm}^2$ ) e razão área da túnica média/área lúmen (MCT vs CTRL: 41,23  $\pm$  1,48 vs 31,97  $\pm$  2,99%). No entanto, no grupo MCT+NRG verificou-se uma atenuação significativa destas alterações (34,26  $\pm$  0,91 mm, 75,64  $\pm$  5,10  $\text{mm}^2$  e 29,56  $\pm$  2,46%, respectivamente).

**Conclusões:** O tratamento crónico com NRG-1 reduziu significativamente os processos fisiopatológicos típicos da HAP, como a disfunção endotelial e a remodelagem da vasculatura pulmonar. Estas observações sugerem que o sistema da NRG-1 desempenha um papel relevante na função vascular no contexto de HAP, constituindo assim um potencial alvo terapêutico.