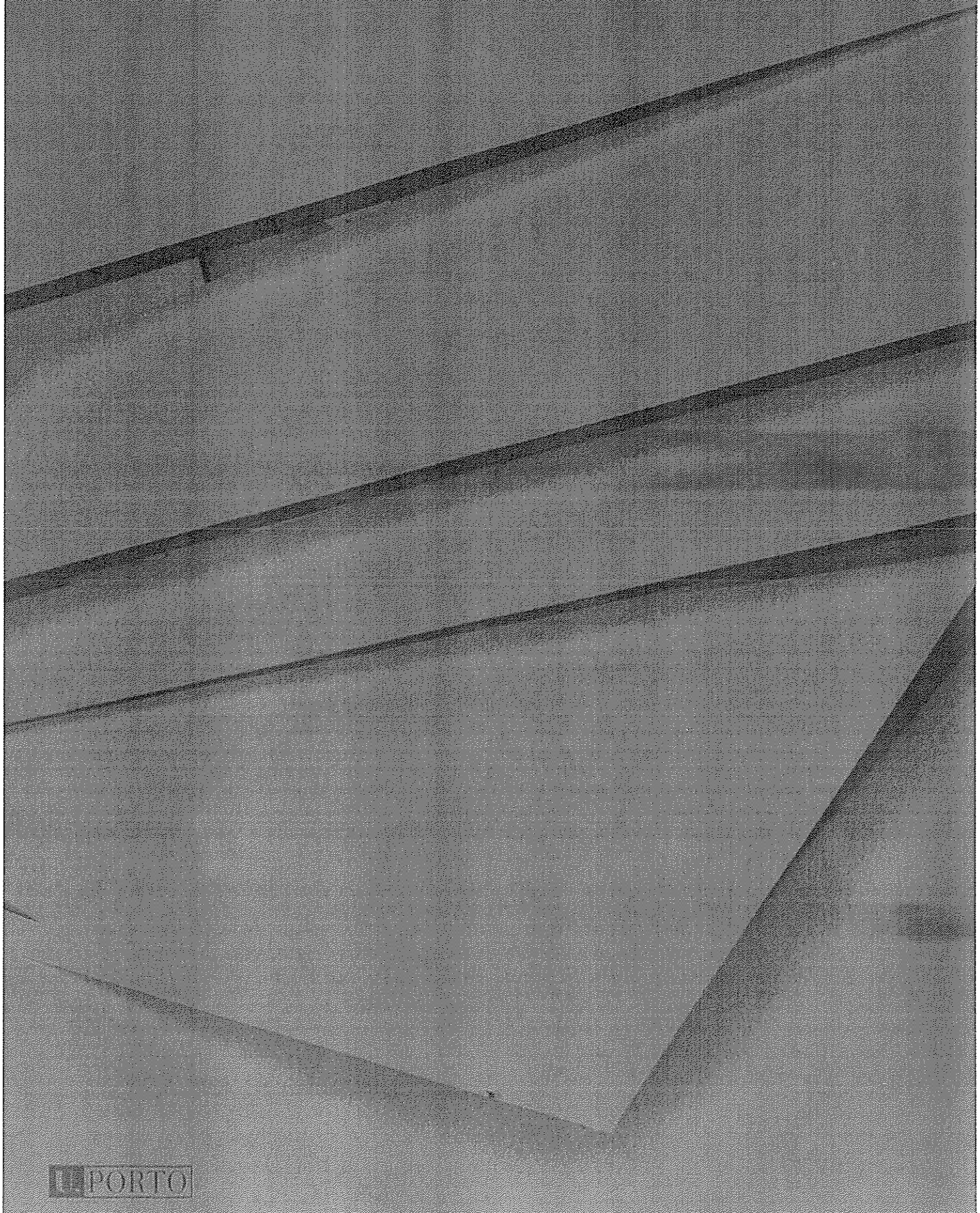
BOOK OF ABSTRACTS

5TH MEETING OF YOUNG RESEARCHERS OF UNIVERSITY OF PORTO

IJUP'12



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IJUP'12

5th MEETING OF YOUNG RESEARCHERS
OF UNIVERSITY OF PORTO

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CREDITS

Livro de Resumos IJUP'12

5º Encontro
de Investigação
Jovem da U.Porto

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Design
Tiago Campeã
Rui Mendonça

Impressão e acabamentos
Invulgar – artes gráficas

Tiragem
1300 exemplares

Depósito Legal
340336/12

ISBN
978-989-8265-82-1

Neuregulin attenuates right ventricular hypertrophy and dysfunction in an experimental model of pulmonary hypertension

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Neuregulin (NRG)-1 is implicated in the preservation of left ventricular (LV) performance in pathophysiological conditions [1]. Nevertheless, the role of NRG-1 in right ventricular (RV) failure secondary to pulmonary arterial hypertension (PAH) is still unknown. This study analysed the effects of NRG-1 chronic treatment in an animal model of PAH and HF.

Male Wistar rats (180-200g) randomly received monocrotaline (MCT, 60mg/Kg, sc) or vehicle. After 14 days, animals from these groups were randomly assigned to receive treatment with either NRG-1 (4ug/Kg/day, ip) or vehicle. The study resulted in 4 groups: control (n=10); control+NRG (n=10); MCT (n=10); MCT+NRG (n=10). Echocardiography, RV invasive hemodynamic evaluation and sample collection were performed 25 to 28 days after MCT administration.

MCT group developed PAH, as shown by the increase in RV maximum pressure (MCT vs control: 63±3 vs 34±3mmHg) and by the decrease in cardiac output (MCT vs control: 34.4±4.4 vs 64.6±3.4mL/min) which were both attenuated in the MCT+NRG group (53±3mmHg and 52.2±1.6mL/min). Ecocardiographic data confirmed these results and showed a marked dilatation of the RV, and a decrease in the pulmonary artery acceleration time in the MCT group, changes that were also reduced by NRG-1 treatment. Animals from the MCT group developed RV hypertrophy (RVweight/tibia length ratio MCT vs control: 0.08±0.002 vs 0.05±0.003 g/cm) and pulmonary congestion (lung weight/tibia length ratio MCT vs control: 0.7±0.03 vs 0.4±0.03g/cm), both changes were minimized by the NRG-1 treatment (0.06±0.002 g/cm and 0.6±0.03 g/cm, respectively). Histological analysis also revealed a decrease of RV cardiomyocyte hypertrophy and fibrosis in the MCT+NRG group in comparison with MCT group.

The RV of MCT group animals presented an increased expression of brain natriuretic peptide (BNP) and endothelin (ET)-1 (17.5 and 5.0 times vs control, respectively). These changes were attenuated or reversed in the MCT-NRG group.

NRG-1 chronic treatment significantly reduced the severity of PAH and RV hypertrophy, as well as the expression of genes associated with overload and ventricular hypertrophy. These findings suggest that the NRG-1 pathway has a relevant role on the pathophysiology of PAH and right ventricular HF, representing a potential therapeutically target.

[1] De Keulenaer GW, Doggen K, Lemmens K. (2010).*The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anticancer therapy.* Circ Res, 106:35-46.