

P07. Diastolic dysfunction in alveolar hypoxia: A role for interleukin-18-induced increase in protein phosphatase 2A and reduction in phospholamban phosphorylation

Larsen K-O^{1,2,3}, Lygren B⁴, Sjaastad I^{2,3,5}, Krobert KA^{3,6}, Arnkværn K^{2,3}, Florholmen G^{2,3}, Ruud Larsen A-K⁷, Levy FO^{3,6}, Taskén K⁴, Skjøsberg OH¹, Christensen G^{2,3}

¹ Department of Pulmonary Medicine, Ullevål University Hospital, Oslo, Norway

² Institute for Experimental Medical Research, Ullevål University Hospital, Oslo, Norway

³ Center for Heart Failure Research, University of Oslo, Oslo, Norway

⁴ The Biotechnology Centre of Oslo, University of Oslo, Oslo, Norway

⁵ Department of Cardiology, Ullevål University Hospital, Oslo, Norway

⁶ Department of Pharmacology, University of Oslo, Oslo, Norway

⁷ Department of Immunology and Transfusion Medicine, Ullevål University Hospital, Oslo, Norway

Introduction: We have previously reported right ventricular (RV) and left ventricular (LV) diastolic dysfunction in mice subjected to alveolar hypoxia, possibly mediated by reduced serine (Ser) 16 phosphorylated phospholamban (PLB).

Hypothesis: Reduction in Ser16 phosphorylated PLB observed in both ventricles during alveolar hypoxia is a result of changes in the β -adrenergic signaling cascade or in protein phosphatases (PP). These changes are caused by a hypoxia-induced increase in levels of circulating mediators.

Methods: In mice exposed to 10 % oxygen for 14 days, signaling molecules were measured in cardiac tissue, isolated sarcoplasmic reticulum (SR) and serum. Cardiomyocytes isolated from neonatal mice were exposed to interleukin (IL)-18 for 24 hours. For measurements of Ser16 phosphorylated PLB in isolated cardiomyocytes, the cells were stimulated with 1 nM isoproterenol for 5 min before harvesting.

Results: The levels of β -adrenergic receptors and β -adrenergic receptor-stimulated adenylyl cyclase activity in the ventricles and the amounts of protein kinase A subunits and A kinase anchoring proteins in SR were not changed. Alveolar hypoxia increased the amounts of SR-associated PP1 and PP2A in the RV (143 ± 16 % and 122 ± 6 %, respectively, $n=7$) and the LV (177 ± 27 % and 124 ± 12 %, respectively, $n=7$) compared to controls. In the LV free wall, which is not exposed to increased after-load, alveolar hypoxia increased both the total PP activity and the PP2A activity to 165 ± 21 % and 271 ± 90 % of respective controls ($n=5$). Screening of an array of cytokines in serum revealed that IL-18 concentrations in serum were substantially increased after 1, 2, 7 and 14 days of hypoxia. IL-18 stimulation increased the amount and the activity of PP2A to 134 ± 13 % ($n=13$) and 122 ± 8 %, respectively, of controls in isolated cardiomyocytes. A reduction in Ser16 phosphorylated PLB to 57 ± 9 % of controls ($n=6$) was measured in isolated cardiomyocytes exposed to IL-18.

Conclusions: Our data indicate that diastolic dysfunction in alveolar hypoxia is caused by reduced Ser16 phosphorylated PLB and increased amounts and activity of protein phosphatase 2A at least partly mediated by elevated levels of IL-18.