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Abstract:

Background: BAY 41-8543 reduces pulmonary vascular resistance and right ventricle injury in experimental PE. Objective: Test if BAY 41-8543 protects pulmonary artery (PA) endothelial function in PE. Methods: PE was induced (anesthetized, Sprague-Dawley rats, 25 µm polystyrene microspheres, 1.95 million/100g, IV) with BAY 41-8543 (50 ug/kg, IV) or solvent treatment. Controls had vehicle for microspheres. Rings isolated from primary PA branches (5hr. PE) were contracted (phenylephrine, 10-6M) and dilation was endothelium-dependent (acetylcholine, 10-7M – 10-5M) or with BAY 41-8543 (10-8M – 10-6M). Oxidant stress was assessed: PA tissue 4-hydroxynoneal (4-HNE) immunohistochemistry; plasma malondialdehyde (MDA). Other Control rings received red blood cell (RBC) lysate. Results: PE inhibited dilation to acetylcholine vs. Control (dose x group interaction p=0.001), while dilation to BAY 41-8543 was minimally changed. PE

raised plasma hemoglobin (30-fold, p=0.003), 4-HNE stain and plasma MDA (2.2-fold, p=0.009). Treating PE rats with BAY 41-8543 reduced plasma hemoglobin, 4-HNE and MDA to levels not different from Control. Dilation to acetylcholine significantly improved in PE + BAY 41-8543 rats vs. PE (dose x group interaction p=0.04). Addition of RBC lysate to Control rings reduced dilation to acetylcholine, while BAY 41-8543 responses remained strong. Conclusion: PE caused PA endothelial dysfunction, elevated plasma hemoglobin and oxidant stress. Treating rats with BAY 41-8543 lowered plasma hemoglobin, oxidant stress and endothelial dysfunction in PE. Treating isolated rings with BAY 41-8543 bypassed endothelial dysfunction with PE or RBC lysate.

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