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Comparative investigation of pulmonary vasodilating effects of inhaled Nitric Oxide (NO) gas therapy and inhalation of SIN-1, a new drug formulation containing an NO-donor metabolite

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Background: The management of acute pulmonary hypertension has recently been in the center of attention as Coronavirus Disease 2019 (COVID-19) might lead to acute respiratory distress syndrome associated with hypoxia-induced pulmonary vasoconstriction. Therefore inhalation therapy has been the object of several clinical trials.

Purpose: In this experimental study we aimed at investigating the hemodynamic effect of inhalative SIN-1a (3-morpholino-syndnonimine, the unstable active metabolite of molsidomine, stabilized by cyclodextrine) administration during physiological and pathological conditions in a large animal model.

Methods: Landrace pigs were randomized into the following experimental groups: iNO (inhaled nitric-oxide, n=3), SIN-1-5 (5 mg, n=3), SIN-1-10 (10 mg, n=3). Hemodynamic parameters were recorded after parallel insertion of PiCCO system and Swan-Ganz catheter. The effect of iNO and SIN-1 inhalation (30 min) was investigated under physiologic conditions and U46619, a thromboxane-receptor agonist induced pulmonary hypertension.

Results: The observed alterations after inhalation therapy were quite similar under physiological and pathological condition. Pulmonary arterial pressure (PAP) was decreased by all of these drugs, SIN-1-10 had similar effect as iNO (physiological contidiont: -36.1% iNO, -23.8% SIN-1-5, -35.5% SIN-1-10; U46619-induced pulmonary hypertension: -30.1% iNO, -22.1% SIN-1-5, -31.2% SIN-1-10). While iNO therapy did not influence the mean arterial pressure (MAP) and systemic vascular resistance (SVR) values, SIN-1 administration resulted in decreased MAP and SVR values. Pulmonary vascular resistance (PVR) was decreased by iNO greater than with using SIN-1. As a result of these alterations, the PVR/SVR ratio decreased markedly in the iNO group, while it was stepwisely increased in the SIN-1-5 and SIN-1-10 group.

Conclusion: The pulmonary vasodilator effect of SIN-1 was dose dependent, and in case of larger dose it was comparable to that of iNO. However, the vasodilatory effects of SIN-1 inhalation was not limited to the pulmonary circulation, a significant and dose-dependent systemic vasodilation could also be documented.