

Title: Inhaled nitric oxide attenuates post-arrest cardiovascular dysfunction and immune response after cardiac arrest in mice

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Introduction: Elevated pulmonary vascular resistance and pulmonary hypertension (PAH) were observed in post-cardiac arrest (CA) patients. Left ventricular (LV) dysfunction with or without concomitant right ventricular (RV) dysfunction were reported to contribute to poor outcomes in post-CA patients. We have previously reported that inhaled nitric oxide (iNO) markedly improved neurological outcome and survival in mice after CA and CPR in a soluble guanylate cyclase $\alpha 1$ (sGC $\alpha 1$)-dependent manner. However, the mechanisms responsible for the protective effects of iNO on cardiovascular (CV) dysfunction after CA/CPR are incompletely understood.

Objective: To elucidate the mechanism of NO inhalation to prevent cardiovascular and neurological dysfunction and improve survival after CA.

Methods and Results: Eight to 12 week-old age- and weight-matched male C57BL/6J wild-type (WT) mice and mice deficient for sGC $\alpha 1$ (sGC $\alpha 1^{-/-}$) were subjected to 8 min of CA by injection of potassium chloride whereupon CPR was performed with chest compression and mechanical ventilation. Starting 1h after CPR, mice breathed air or NO at 40 ppm for 24 h. To determine the mechanisms responsible for the beneficial effects of iNO, cardiac function and PAH (estimated by RV systolic pressure) were measured by echocardiography. iNO attenuated impairment of LV dysfunction and PAH after CA in WT mice, but not in sGC $\alpha 1^{-/-}$ mice (Figure a, b). These results suggest that iNO prevents CA-induced CV dysfunction via sGC $\alpha 1$ -dependent mechanisms. To examine effects of iNO on immunological reaction induced by CA/CPR, mice blood were obtained at 24 h after CA and analyzed for the complete blood counts with leukocyte differential analysis. We found that polymorphonuclear leukocyte (PMN) in the peripheral blood markedly increased 24 h after CA, suggesting that innate immune system is potential aggravating factor in the post-CA syndrome. iNO attenuated the increased circulating PMN in WT, but not in sGC $\alpha 1^{-/-}$ mice (Figure c). These results indicate that iNO prevents increase of PMN after CA/CPR via sGC-dependent mechanisms.

Conclusion: These results suggest that the iNO attenuates post-arrest CV dysfunction and innate immune response in a sGC-dependent manner thereby improving outcomes in a murine model of CA/CPR. Further elucidation of the mechanism of action of iNO/sGC will accelerate the translation of this promising therapy.

Figure legend: iNO prevented (a) the increase of RVSP at 6 h after CA, (b) LV dysfunction at 24 h after CA and (c) the increase of polymorphonuclear leukocyte (PMN) at 24 h after CA in an sGC α_1 -dependent manner. *P<0.05, ** P<0.01, *** P<0.001 between each group. n = 5-8.

