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Breathing nitric oxide plus hydrogen gas reduces ischemia–reperfusion injury and nitrotyrosine production in murine heart

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Abstract

Inhaled nitric oxide (NO) has been reported to decrease the infarct size in cardiac ischemia-reperfusion (I/R) injury. However, reactive nitrogen species (RNS) produced by NO cause myocardial dysfunction and injury. Because H_2 is reported to eliminate peroxynitrite, it was expected to reduce the adverse effects of NO. In mice, left anterior descending coronary artery ligation for 60 min followed by reperfusion was performed with inhaled NO [80 parts per million (ppm)], H_2 (2%), or NO + H_2, starting 5 min before reperfusion for 35 min. After 24 h, left ventricular function, infarct size, and area at risk (AAR) were assessed. Oxidative stress associated with reactive oxygen species (ROS) was evaluated by staining for 8-hydroxy-2'-deoxyguanosine and 4-hydroxy-2-nonenal, that associated with RNS by staining for nitrotyrosine, and neutrophil infiltration by staining for granulocyte receptor-1. The infarct size/AAR decreased with breathing NO or H_2 alone. NO inhalation plus H_2 reduced the infarct size/AAR, with significant interaction between the two, reducing ROS and neutrophil infiltration, and improved the cardiac function to normal levels. Although nitrotyrosine staining was prominent after NO inhalation alone, it was eliminated after breathing a mixture of H_2 with NO. Preconditioning with NO significantly reduced the infarct size/AAR, but not preconditioning with H_2. In conclusion, breathing NO + H_2 during I/R reduced the infarct size and maintained cardiac function, and reduced the generation of myocardial nitrotyrosine associated with NO inhalation. Administration of NO + H_2 gases for inhalation may be useful for planned coronary interventions or for the treatment of I/R injury.

Keywords: antioxidants; hydrogen gas; ischemia; nitric oxide; reperfusion injury.

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