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WHAT'S NEW IN INTENSIVE CARE

Electrically generated nitric oxide from air: a safe and economical treatment for pulmonary hypertension

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Electrically generated nitric oxide

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator approved by the US Food and Drug Administration in 1999 for the treatment of persistent pulmonary hypertension of the newborn [1]. The current NO delivery system is large, heavy, cumbersome and expensive, requires a cylinder distribution network and a device to regulate NO levels, monitor nitrogen dioxide (NO_2), percent of O_2, and trained respiratory therapy staff. Several methods have been used to produce NO for biomedical applications, including chemical and electrical systems. However, these methods produce large amounts of NO_2 and ozone (O_3) toxic byproducts, requiring complex purification systems. Recently, we designed, developed, and tested a lightweight, portable, economical device generating NO by pulsed electrical discharge in air using a high-voltage resonant power supply, to produce low levels of NO_2 and O_3 [2]. The electrodes are powered by a microcontroller circuit. Energy is stored and released by an autotransformer and delivered to the spark gap to create a plasma. The levels of NO can be controlled by electrical variables. Our previous studies demonstrated that NO can be generated continuously and stably by one set of electrodes at a desired concentration for at least 1 month [2]. We selected iridium electrodes for NO generation to reduce the level of NO_2 when compared to other metal electrodes. Using a 12-g scavenger, we removed NO_2 and O_3, and demonstrated that the electrical plasma NO generator stably produces safe therapeutic levels of inhaled NO from air [3]. Recently, we have developed a novel miniaturized version of the device for an infant, weighing about 14-g and safely producing therapeutic levels of NO from air [4]. Several advantages of using electrically generated NO include (1) lightweight (versus a cylinder), which makes possible ambulatory applications, such as in remote areas or the battle field, (2) relatively low power is needed to generate desired concentrations of NO gas (e.g. power 5–6 watts for 80 ppm NO), which makes it possible to power the device by batteries, (3) economical, which will enable increased accessibility to NO treatment, including patients in developing countries (Table 1). Several pre-clinical studies have been completed to confirm the effectiveness, safety, and feasibility of electrically generated NO (described in the ESM).

Clinical values and potential applications in the developing countries

The high cost of providing NO and its complex cylinder delivery system limit this life-saving inhaled NO therapy for in-hospital use to well-equipped medical centers in developed countries. In contrast, electrical generation of NO from air provides a simple, safe, and economical solution. NO may play an important role in treating a broad spectrum of diseases, such as in cardiac surgery, heart–lung transplantation, pediatric acute respiratory distress syndrome (ARDS), cerebral malaria, blood transfusion, and cystic fibrosis [5, 6].

A randomized clinical trial of 244 Chinese adults undergoing elective, multiple valve replacement surgery, due mostly to rheumatic fever, administration of 80 ppm of NO during and after prolonged cardiopulmonary bypass (CPB) reduced the incidence of acute kidney injury and decreased the rate of chronic kidney disease at 1 year follow-up after surgery [7]. In a

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Table 1 Features and potential indications of electrical NO generator

Features	Bench-top NO generator (fixed)	Mini-NO generator (portable)
Size (cm^3)	35·25·12 (L·W·H)	18·12·8 (L·W·H)
Weight (kg)	4	< 1
Scavenger required (g)	12	0.8
Power required (Watts)	5–6	2–3
Electrodes	Iridium–platinum	Iridium–iridium
Modality in NO generation	Continuous	Continuous or intermittent (only during inspiration)
Indications	ICU, respiratory unit, cardiac surgery, cardiopulmonary bypass	Chronic heart and lung diseases
Application areas	Inside hospital	Ambulatory settings, e.g. home, helicopter, remote areas, or battle field

randomized controlled trial, 101 children undergoing CPB, delivering 20 ppm of NO through the oxygenator reduced the frequency of developing low cardiac output syndrome and decreased the use of extracorporeal membrane oxygenation (ECMO) [8]. Breathing NO (40 ppm, 68 days), as a bridge to heart–lung transplantation, in a patient with end-stage pulmonary hypertension revealed no significant toxicity in the explanted lung [9]. In another patient with end-stage idiopathic pulmonary fibrosis and pulmonary hypertension, inhalation of 20 ppm NO for 30 months while waiting for lung transplantation, significantly improved arterial oxygenation and pulmonary arterial pressure [10]. In children with ARDS, inhaling NO as low as 5 ppm was associated with a significantly reduced duration of mechanical ventilation and greater rate of ECMO–free survival [11]. Similarly, breathing 20 ppm of NO for at least 1 h, decreased the average number of days that patients required ventilator support via reduced use of high-frequency oscillatory ventilation and ECMO, and thus reduced hospital charges in 98 children with ARDS [12]. In Uganda et al. demonstrated that breathing NO from cylinders for 48 h was safe in a randomized open-label, phase II, controlled trial of breathing 80 ppm NO in air or air alone in 92 children with cerebral malaria [13]. In blood transfusion, studies have shown that breathing NO (5–80 ppm) prevents pulmonary hypertension induced by infusion of hemoglobin-based oxygen carriers (HBOCs) or red blood cells stored for prolonged time [5, 14]. The administration of inhaled NO (20–80 ppm) from cylinders combined with 2 units of HBOC infusion prevented pulmonary and systemic vasoconstriction, improved cardiac output, arterial oxygen content, and lactate clearance in a patient with acute life-threatening anemia [15]. Berra and co-workers demonstrated in human volunteers that inhalation of NO prevented pulmonary hypertension associated with the transfusion of autologous leukoreduced blood stored for 40 days [16]. Recently, a prospective, open-label pilot study in cystic fibrosis patients with refractory mycobacterium abscessus lung infection, reported that breathing NO (160 ppm, 30-min each, every 4 h for 7–14 days) is well tolerated, safe, and led to an increased 6-min walk distance and forced expiratory volume in 1-s after NO treatment [17].

In summary, inhaled NO produces selective pulmonary vasodilation without reducing systemic vascular resistance or systemic arterial pressure. With the recent break-through invention and testing of an electrical NO generator from air, inhaled NO should become affordable and accessible to patients in developing countries where cylinder NO gas is not available. Furthermore, this portable NO generator is likely to expand the indications for inhaled NO therapy, especially for patients with pulmonary hypertension and chronic lung disease in the ambulatory setting. The future direction for developing the electric NO generator will be miniaturized prototype. An ideal electric NO generator, like a pacemaker, could be implanted into a patient's trachea or NO delivered via a transtracheal Scoop catheter directly to the airway to save energy, electrodes, and reduce scavenger consumption.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
B.Y. and W.M.Z. have patents at MGH on the electric generation of nitric oxide (NO). W.M.Z. is on the scientific advisory board of Third Pole Inc., which has licensed patents on NO generators from MGH. Other authors declare no conflicts of interest.

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