Nitric Oxide 60 (2016) 16–23

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Detection and removal of impurities in nitric oxide generated from air by pulsed electrical discharge

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ARTICLE INFO

Article history:
Received 24 May 2016
Received in revised form
5 August 2016
Accepted 29 August 2016
Available online 31 August 2016

Keywords:
Nitric oxide
Pulsed electrical discharge
Metal particles
Iridium electrode

ABSTRACT

Inhalation of nitric oxide (NO) produces selective pulmonary vasodilation without dilating the systemic circulation. However, the current NO/N_2 cylinder delivery system is cumbersome and expensive. We developed a lightweight, portable, and economical device to generate NO from air by pulsed electrical discharge. The objective of this study was to investigate and optimize the purity and safety of NO generated by this device. By using low temperature streamer discharges in the plasma generator, we produced therapeutic levels of NO with very low levels of nitrogen dioxide (NO_2) and ozone. Despite the low temperature, spark generation eroded the surface of the electrodes, contaminating the gas stream with metal particles. During prolonged NO generation there was gradual loss of the iridium high-voltage tip (−90 μg/day) and the platinum-nickel ground electrode (−55 μg/day). Metal particles released from the electrodes were trapped by a high-efficiency particulate air (HEPA) filter. Quadrupole mass spectroscopy measurements of effluent gas during plasma NO generation showed that a single HEPA filter removed all of the metal particles. Mice were exposed to breathing 50 parts per million of electrically generated NO in air for 28 days with only a scavenger and no HEPA filter; the mice did not develop pulmonary inflammation or structural changes and iridium and platinum particles were not detected in the lungs of these mice. In conclusion, an electric plasma generator produced therapeutic levels of NO from air; scavenging and filtration effectively eliminated metallic impurities from the effluent gas.

1. Introduction

Nitric oxide (NO) is a selective pulmonary vasodilator that was approved by the U.S. Food and Drug Administration in 1999 for the treatment of hypoxic term or near-term newborns with persistent pulmonary hypertension (PPHN) [1]. Since approval, inhaled NO has predominantly been used in major medical centers of the developed world to treat pulmonary hypertension in newborns, and children and adults with pulmonary hypertension [2–5]. By 2015, an estimated half million American children and adults with pulmonary hypertension of diverse etiology had been treated with inhaled NO [6,7]. Wider use of NO therapy is significantly limited, however, because the current delivery systems are cumbersome and expensive, requiring compressed gas cylinders, a cylinder distribution network, a complex delivery device, gas monitoring

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http://dx.doi.org/10.1016/j.niox.2016.08.005
1089-8603/

and calibration devices, and trained respiratory therapy staff. For many hospitals, inhaled NO is one of the most expensive drugs used in neonatal medicine [8]; the average cost of providing NO therapy for 5 days to a newborn patient with PPHN at Massachusetts General Hospital (MGH) is approximately $14,000. The high cost and difficulties associated with delivery have limited the use of NO in the ambulatory setting and the potential benefits of chronic NO inhalation in non-hospitalized patients have not been thoroughly investigated.

Both chemical and electric plasma discharge methods have been used to produce NO for biomedical purposes [9–11]. However, these methods produce large amounts of toxic byproducts, such as nitrogen dioxide (NO_2) and ozone (O_3), requiring complex purification systems [12,13]. Recently, we designed, developed, and tested in lambs a lightweight, economic, and portable NO generation system using pulsed electrical discharge [14]. The prototype NO generation system produced a therapeutic range of NO (5–80 parts per million (ppm)) in air or an oxygen-enriched nitrogen containing gas [14]. Iridium or other noble metal electrodes produced the lowest fractional amount of NO_2/NO compared to nickel, carbon or tungsten electrodes [14]. Iridium is a rare and inert metal. Very little is known about the toxicity of inhaled iridium aerosols, and data on the toxicity of inhaled iridium in human studies are not available. Platinum is also a noble metal and is non-reactive. There are no data on toxicity of inhalation of platinum aerosols in humans. However, inhalation of nickel aerosols can cause toxic effects in the respiratory tract and immune system [15–17]. To minimize the production of potentially harmful gases (NO_2) and the release of metal particles from the surface of the electrodes, we focused on using low temperature sparks with low current flows in the plasma.

The objective of this study was to detect, and if necessary remove, potentially harmful particles produced by the electric plasma NO generator. First, we sought to determine whether electrodes underwent erosion after prolonged NO generation. Because electrode erosion was detected by scanning electron microscopy (SEM), we determined the chemical composition of particles released from the electrode using energy-dispersive X-ray spectroscopy (EDX). Second, we characterized the temperature of the plasma during NO generation to better characterize the erosion process. Third, we tested whether a 0.22 μm high-efficiency particulate air (HEPA) filter, placed in series with the NO generator, would capture metal particles in the effluent gas stream. Finally, we investigated whether any pathologic effects or metal particles were detected in murine airways and lung tissues after mice breathed electrically generated NO (50 ppm) in air for 28 days with only a $Ca(OH)_2$ scavenger (to remove NO_2) but no particulate air filter.

2. Materials and methods

2.1. Determination of metallic components of electrodes

The electrodes are composed of a high voltage tip and a ground electrode. We used SEM to detect morphological changes in the electrodes and EDX to determine the composition of the surface metallic components of the tip and ground electrodes.

2.2. Measurement of electrode erosion

SEM was used to image the high voltage tip and the ground electrode (ACDelco 41–101, AutoZone) before (new) and after 7, 10, or 28 days of continuous plasma NO production. Four pulse pattern control variables were selected to precisely control the levels of NO production. These variables included the number of spark groups per second (B), the number of spark discharges per group (N), the time in microseconds (μsec) between two spark discharges (P), and the pulse time in μsec (H) (14). Specifically, to synthesize 50 ppm NO at 5 L/min airflow, B was set at 20, N at 30, P at 240, and H at 70. The electrode gap was set at 2 mm (see schematic of bench testing apparatus in online supplement Fig. 1). Prior to imaging, electrodes were ultrasonically cleaned with a mixture of 70% ethyl alcohol and 30% deionized water. All images of the electrodes were obtained using secondary-electron emissions in a high vacuum. Photographs of the electrode surfaces were taken either topographically or in cross section. The SEM accelerating voltage varied between 5 and 20 kV. To calculate mass (M) changes of the electrodes before (new) and after NO generation, we used the formula: $M = \rho\pi d^2 h/4$ (ρ density, d diameter, h height).

2.3. Optical diagnostics and determination of discharge temperatures

Light emitted from the electrical discharge was collected using a fiberoptic bundle (Princeton Instruments-Acton, 10 fibers −200 μm core) connected to a spectrometer (Princeton Instruments – Acton Research, TriVista TR555 spectrometer system with PIMAX digital ICCD camera, Trenton, NJ). The spectrum was integrated over a 5 s interval. Because the discharge was non-equilibrium, the gas temperature was estimated by determining the rotational temperature from the spectrum of nitrogen due to fast collisional relaxation at atmospheric pressure [18]. One of the most reliable ways of measuring heavy particles (gas) temperature in non-thermal plasma is based on analysis of the nitrogen second positive system. Equating the rotational temperature Tr (C) of the C state and Tr (X) of the ground state of nitrogen is valid in the case of a non-equilibrium plasma. Due to the long residence time, the nitrogen ground state is in rotational–translational equilibrium with the host gas. Because the change in rotational angular momentum is small during electron impact excitation, the ground state rotational distribution is transferred to the nitrogen (C) state. The rotational temperature of nitrogen is determined by fitting a synthetic spectrum to the experimental spectrum of the (0–2) transition emission bands of the second positive system of nitrogen at 337 nm with the program SPECAIR 3.0 [19].

2.4. Detecting metal particles deposited on a HEPA filter

A 0.22 μm HEPA filter (5708, HEPA, Vital Signs Inc., Totowa, NJ) located downstream of the NO generator was used to capture metal particles during NO generation. SEM imaging and EDX were used to detect and identify metal particles on the upstream and downstream surfaces of the HEPA filter. A JSM-6010LA SEM (JEOL Ltd., Tokyo, Japan) was used for SEM imaging and EDX analysis. Back-Scattered Electron (BSE) imaging of filters was performed in a low vacuum mode. The inflow and outflow surfaces of the filter were imaged and an image of the filter in cross section was obtained after transecting the filter with a blade.

2.5. Detection and measurement of metal particles emitted by the plasma NO generation device

Quadrupole inductively-coupled plasma mass spectrometry (ICP-MS, iCAP Qc, Thermo Fisher, Bremen, Germany) was used to determine the nature and quantity of metal particles released by the plasma discharge from the electrodes while the device generated NO at an airflow of 0.05 L/min (medical grade air, Airgas, Cambridge, MA). Argon gas (0.95 L/min) was mixed with air (0.05 L/min), and then injected into the ICP-MS (producing 5% medical grade air mixed with 95% argon, see online supplement Fig. 2). The level of NO production by the metal electrodes was controlled by