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Systems and methods for synthesis of nitric oxide

Abstract

Systems and methods for producing nitric oxide (NO) to be used in medical applications are provided. In some embodiments, systems and methods are provided for a NO generator that is capable of generating a desired concentration of NO to be provided to a respiratory system for inhalation by a patient.

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Background/Summary

CROSS-REFERENCES TO RELATED APPLICATIONS (1) The present application is a continuation of U.S. patent application Ser. No. 15/520,137, filed on Apr. 19, 2017 and issued on Nov. 15, 2022 as U.S. Pat. No. 11,497,878, which represents the national stage entry of International Application PCT/US2015/056443, filed on Oct. 20, 2015, which is based on, claims priority to, and incorporates herein by reference in their entirety, U.S. Provisional Patent Application No. 62/065,825, filed Oct. 20, 2014, and entitled “Producing Nitric Oxide for Inhalation by Electric Discharge in Air,” and U.S. Provisional Patent Application No. 62/077,806, filed Nov. 10, 2014, and entitled “Synthesis of Nitric Oxide.”

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH
(1) Not Applicable.
BACKGROUND
(2) The disclosure relates generally to the electrical plasma synthesis of nitric oxide (NO) from gases and, more specifically, to systems and methods for producing safe NO to be used in medical applications.
(3) NO is a crucial mediator of many biological systems, and is known to control the level of systemic and pulmonary artery blood pressure, help the immune system kill invading parasites that enter cells, inhibit the division of cancer calls, transmit signals between brain cells, and contribute

to the death of brain cells that debilitates people with strokes or heart attacks, among other things. NO mediates the relaxation of smooth muscle present, for example, in the walls of blood vessels, bronchi, the gastrointestinal tract, and urogenital tract. Administration of NO gas to the lung by inhalation has been shown to produce localized smooth muscle relaxation within the lung's blood vessels and is widely used to treat pulmonary hypertension, pneumonia, hypoxemic respiratory failure of a newborn, etc. without producing systemic side effects.

(4) Inhaling NO can immediately produce potent and selective pulmonary vasodilation that improves the matching of ventilation with perfusion, thereby increasing an injured lung's oxygen transport efficiency, and breathing NO can raise the arterial oxygen tension. Breathing NO produces the rapid onset of pulmonary vasodilator action occurring within seconds of commencing breathing with the absence of systemic vasodilatation, once inhaled, NO diffuses through the pulmonary vasculature into the bloodstream, where it is rapidly inactivated by combination with hemoglobin (the NO dioxygenation reaction). Therefore, the vasodilatory effects of inhaled NO are limited to these pulmonary therapeutic advantages in the treatment of acute and chronic pulmonary hypertension. Inhaled NO can also be used to prevent ischemia reperfusion injury after percutaneous coronary intervention in adults with heart attacks. Furthermore, inhaled NO can produce systemic anti-inflammatory and anti-platelet effects by increasing the levels of circulating NO biometabolites and by other mechanisms, such as the oxidation of circulating ferrous hemoglobin in the plasma. Finally, NO has known anti-microbial activity.

BRIEF SUMMARY

(5) The present disclosure provides systems and methods for producing nitric oxide (NO) to be used in medical applications. Specifically, systems and methods are provided for a NO generator that is capable of generating a desired concentration of pure and safe NO to be provided to a respiratory system for inhalation by a patient.

(6) In one aspect, the present disclosure provides an apparatus for generating nitric oxide including one or more pairs of electrodes, a filter arranged downstream of the electrodes, and a scavenger arranged downstream of the electrodes. The apparatus further includes one or more sensors configured to measure at least one of a flowrate of gas, an oxygen concentration upstream of the electrodes, a nitric oxide concentration downstream of the scavenger, and a nitrogen dioxide concentration downstream of the scavenger, and a controller in communication with the electrodes and the one or more sensors and configured to supply an electrical signal to the electrodes that controls timing and sparking characteristics of the electrodes. The sparking characteristics of the electrodes determine a concentration of nitric oxide generated by the electrodes.

(7) In some embodiments, the electrodes comprise at least one of tungsten carbide, carbon, nickel, iridium, titanium, rhenium, and platinum

(8) In some embodiments, the electrodes comprise iridium.

(9) In some embodiments, the scavenger is fabricated from calcium hydroxide.

(10) In some embodiments, the one or more sensors include an airway flowmeter arranged downstream of the electrodes, an oxygen sensor arranged upstream of the electrodes, a nitric oxide sensor arranged downstream of the scavenger, and a nitrogen dioxide sensor arranged downstream of the scavenger.

(11) In some embodiments, an ignition coil is in communication with the controller and the electrodes.

(12) In some embodiments, the controller is further configured to instruct the ignition coil to supply stored electrical energy to the electrodes.

(13) In some embodiments, the electrical signal supplied to the electrodes controls at least one of a number of electrode spark groups per second, a number of individual electrode sparks per spark group, a time between individual electrode sparks, and a pulse duration.

(14) In some embodiments, the controller is further configured to vary at least one of the number of electrode spark groups per second, the number of individual electrode sparks per spark group, the

time between individual electrode sparks, and the pulse duration in response to feedback from the one or more sensors.
(15) In some embodiments, the apparatus further comprises a gas pump arranged upstream of the electrodes.
(16) In some embodiments, the one or more sensors provide an indication of inspiration.
(17) In some embodiments, the controller is further configured to supply the electrical signal to the electrodes in response to detecting inspiration.
(18) In some embodiments, the filter is configured to filter particles flowing downstream of the electrodes with a diameter greater than approximately 0.22 micrometers.
(19) In another aspect, present disclosure provides an apparatus for generating nitric oxide to be integrated into a respiratory system having a breathing apparatus, an inspiratory line, and an airway flowmeter arranged on the inspiratory line. The apparatus includes one or more pairs of electrodes in gaseous communication with the inspiratory line, a filter arranged downstream of the electrodes, and a scavenger arranged downstream of the electrodes. The apparatus further includes one or more sensors configured to measure at least one of an oxygen concentration upstream of the electrodes, a barometric pressure, a nitric oxide concentration downstream of the scavenger, and a nitrogen dioxide concentration downstream of the scavenger, and a controller in communication with the electrodes, the one or more sensors, and the airway flowmeter; and configured to supply an electrical signal to the electrodes that controls timing and sparking characteristics of the electrodes. The sparking characteristics of the electrodes determine a concentration of nitric oxide generated by the electrodes.
(20) In some embodiments, the electrodes are arranged between an inlet and an outlet, the outlet is coupled to the inspiratory line.
(21) In some embodiments, the electrodes are at least partially integrated into the inspiratory line.
(22) In some embodiments, the filter is arranged on the inspiratory line.
(23) In some embodiments, the scavenger is arranged on the inspiratory line.
(24) In some embodiments, the electrodes comprise at least one of tungsten carbide, carbon, nickel, iridium, titanium, rhenium, and platinum.
(25) In some embodiments, the electrodes comprise iridium.
(26) In some embodiments, the scavenger is fabricated from calcium hydroxide.
(27) In some embodiments, the one or more sensors include an oxygen sensor arranged upstream of the electrodes, a nitric oxide sensor arranged downstream of the scavenger, and a nitrogen dioxide sensor arranged downstream of the scavenger.
(28) In some embodiments, an ignition coil is in communication with the controller and the electrodes.
(29) In some embodiments, the controller is further configured to instruct the ignition coil to supply stored electrical energy to the electrodes.
(30) In some embodiments, the electrical signal supplied to the electrodes controls at least one of a number of electrode spark groups per second, a number of individual electrode sparks per spark group, a time between individual electrode sparks, and a pulse duration.
(31) In some embodiments, the controller is further configured to vary at least one of the number of electrode spark groups per second, the number of individual electrode sparks per spark group, the time between individual electrode sparks, and the pulse duration in response to feedback from the one or more sensors.
(32) In some embodiments, the apparatus further comprises a gas pump arranged upstream of the electrodes.
(33) In some embodiments, the airway flowmeter provides an indication of inspiration.
(34) In some embodiments, the controller is further configured to supply the electrical signal to the electrodes in response to detecting inspiration.
(35) In some embodiments, the filter is configured to filter particles flowing downstream of the

electrodes with a diameter greater than approximately 0.22 micrometers.
(36) In some embodiments, the breathing apparatus comprises one of a ventilator system, a continuous positive airway pressure (CPAP) system, a high frequency oscillatory ventilator (HFOV), a face mask, a nasal cannula, or an inhaler.
(37) In still another aspect, the present disclosure provides an apparatus for generating nitric oxide to be integrated into a respiratory system having a breathing apparatus and an inspiratory line. The apparatus includes a chamber having a chamber inlet and at least one or more pairs of electrodes arranged within the chamber, a main chamber configured to provide a fluid path to an airway of a patient. The apparatus further includes a filter arranged downstream of the electrodes, a scavenger arranged downstream of the electrodes, and one or more sensors configured to measure at least one of an oxygen concentration upstream of the electrodes, a barometric pressure, a nitric oxide concentration downstream of the scavenger, and a nitrogen dioxide concentration downstream of the scavenger. The apparatus further includes a controller in communication with the electrodes and the one or more sensors. The controller is configured to supply an electrical signal to the electrodes that controls timing and sparking characteristics of the electrodes. The chamber is in communication with the main chamber and gas in the chamber is non-mechanically introduced into the main chamber.
(38) In some embodiments, the main chamber includes a venturi.
(39) In some embodiments, the apparatus further comprises a passage connecting the chamber to the venturi of the main chamber.
(40) In some embodiments, a flow of gas through the venturi is configured to draw a vacuum on the chamber.
(41) In some embodiments, the apparatus further comprises a pre-scavenger arranged upstream of the chamber inlet.
(42) In some embodiments, the apparatus further comprises a pre-filter arranged upstream of the chamber inlet.
(43) In some embodiments, the main chamber and the chamber define a parallel path.
(44) In yet another aspect, the present disclosure provides a method of generating nitric oxide in a respiratory system having a breathing apparatus in communication with an airway of a patient. The method includes coupling a nitric oxide generator having a pair of electrodes to the airway of the patient, triggering the nitric oxide generator to produce a desired concentration of nitric oxide gas, and determining desired sparking characteristics of the electrodes to produce the desired concentration of nitric oxide gas. The method further includes once the sparking characteristics have determined, supplying an electrical signal to the electrodes that initiates the desired sparking characteristics between the electrodes to generate the desired concentration of nitric oxide gas in a flow of gas provided to the airway of the patient.
(45) In some embodiments, triggering the nitric oxide generator to produce a desired concentration of nitric oxide gas comprises monitoring at least one of a gas flowrate provided to the patient, a temperature of gas provided to the patient, and a pressure of gas provided to the patient, detecting a change in at least one of the gas flowrate provided to the patient, the temperature of gas provided to the patient, and the pressure of gas provided to the patient, and determining that the change detected is indicative of an inspiratory event.
(46) In some embodiments, the method further comprises filtering particulates in the flow of gas provided to the patient.
(47) In some embodiments, the method further comprises scavenging at least one of nitrogen dioxide and ozone in the flow of gas provided to the patient.
(48) In some embodiments, determining desired sparking characteristics of the electrodes comprises measuring an atmospheric pressure, and determining a number of electrode spark groups per second, a number of individual electrode sparks per spark group, a time between individual electrode sparks, and a pulse duration.

(49) In some embodiments, the method further comprises monitoring a nitric oxide concentration downstream of the electrodes, determining that the nitric oxide concentration is not equal to the desired concentration of nitric oxide, and in response to determining that the nitric oxide concentration downstream of the electrodes is not equal to the desired nitric oxide concentration, varying via the electrical signal, at least one of a number of electrode spark groups per second, a number of individual electrode sparks per spark group, a time between individual electrode sparks, and a pulse duration.
(50) In some embodiments, the method further comprises monitoring a nitrogen dioxide concentration downstream of the electrodes, determining that the nitrogen dioxide concentration is greater than a pre-defined maximum concentration, and upon determining that the nitrogen dioxide concentration downstream of the electrodes is greater than the pre-defined maximum concentration, ceasing the supplying of the electrical signal to the electrodes.
(51) The foregoing and other aspects and advantages of the invention will appear from the following description. In the description, reference is made to the accompanying drawings which form a part hereof, and in which there is shown by way of illustration a preferred embodiment of the invention. Such embodiment does not necessarily represent the full scope of the invention, however, and reference is made therefore to the claims and herein for interpreting the scope of the invention.

Description

BRIEF DESCRIPTION OF DRAWINGS
(1) The invention will be better understood and features, aspects and advantages other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such detailed description makes reference to the following drawings.
(2) FIG. **1** shows a schematic illustration of a respiratory system according to one embodiment of the present invention.
(3) FIG. **2** shows a detailed schematic of a nitric oxide generator in the respiratory system of FIG. **1** according to one embodiment of the present disclosure.
(4) FIG. **3** shows an electrical signal applied to electrodes of the nitric oxide generator of FIG. **2** according to one embodiment of the present disclosure.
(5) FIG. **4** shows a schematic illustration of a respiratory system according to another embodiment of the present invention.
(6) FIG. **5** shows a detailed schematic of a nitric oxide generator in the respiratory system of FIG. **4** according to another embodiment of the present disclosure.
(7) FIG. **6** shows one implementation of the nitric oxide generator of FIG. **5** according to one embodiment of the present disclosure.
(8) FIG. **7** shows a respiratory system according to yet another embodiment of the present disclosure.
(9) FIG. **8** shows a respiratory system according to still another embodiment of the present disclosure.
(10) FIG. **9** is a flowchart illustrating steps for operating a respiratory system according to the present disclosure.
(11) FIG. **10** shows a schematic used for testing a nitric oxide generator according to one embodiment of the present disclosure.
(12) FIG. **11** shows a graph illustrating concentrations of NO and NO2 generated while testing the nitric oxide generator of FIG. **2**.
(13) FIG. **12** shows a graph illustrating NO and NO2 concentrations generated by the nitric oxide generator of FIG. **2** over the 10 day test.

(14) FIG. **13**A shows a graph illustrating the effect of varying number of spark groups per second on NO and NO2 concentration for the nitric oxide generator of FIG. **2**.
(15) FIG. **13**B shows a graph illustrating the effect of varying number of spark discharges per group on NO and NO2 concentration for the nitric oxide generator of FIG. **2**.
(16) FIG. **13**C shows a graph illustrating the effect of varying time between spark discharges on NO and NO2 concentration for the nitric oxide generator of FIG. **2**.
(17) FIG. **13**D shows a graph illustrating the effect of pulse duration on NO and NO2 concentration for the nitric oxide generator of FIG. **2**.
(18) FIG. **14** shows a graph illustrating NO and NO2 concentrations generated by the nitric oxide generator of FIG. **2** at varying atmospheric pressures.
(19) FIG. **15** shows a graph illustrating the NO and NO2 concentrations entering and exiting a scavenger following and in series with the nitric oxide generator of FIG. **2**.
(20) FIG. **16** shows a graph illustrating the NO and NO2 concentrations entering and exiting a scavenger of the nitric oxide generator of FIG. **5**.
(21) FIG. **17** shows a graph illustrating the ozone (O3) concentrations entering and exiting a scavenger of the nitric oxide generator of FIG. **2**.
(22) FIG. **18**A shows a magnified view of an unused electrode tip.
(23) FIG. **18**B shows a magnified view of the electrode tip of FIG. **18**A after continuous sparking for 10 days.
(24) FIG. **19**A shows a magnified view of an unused filter.
(25) FIG. **19**B shows a magnified view of the filter of FIG. **19**A after being arranged downstream of electrodes continuously sparking for 10 days.
(26) FIG. **20**A shows a graph illustrating the energy-dispersive X-ray (EDX) spectroscopy results of the filter of FIG. **19**A
(27) FIG. **20**B shows a graph illustrating the energy-dispersive X-ray (EDX) spectroscopy results of the filter of FIG. **19**B.
(28) FIG. **21** shows a graph illustrating the NO2/NO ratio generated by electrodes fabricated from various metals.
(29) FIG. **22** shows a graph illustrating the NO and NO2 concentrations generated with and without a microporous membrane covering the nitric oxide generator of FIG. **5**.
(30) FIG. **23**A shows a graph illustrating the mean pulmonary artery pressure (PAP) of an anesthetized lamb with acute pulmonary hypertension due to U46619 infusion following inhalation of nitric oxide generated using the respiratory system of FIG. **1** and compared with nitric oxide delivered from a compressed NO/N2 gas cylinder.
(31) FIG. **23**B shows a graph illustrating the pulmonary vascular resistance index (PAP) of an anesthetized lamb with acute pulmonary hypertension following inhalation of nitric oxide generated using the respiratory system of FIG. **1** and compared with nitric oxide delivered from a compressed NO/N2 gas cylinder.
(32) FIG. **24**A shows a graph illustrating the mean pulmonary artery pressure (PAP) of an anesthetized lamb with acute pulmonary hypertension following inhalation of nitric oxide generated using the respiratory system of FIG. **4** with the nitric oxide generator continuously sparking and compared with nitric oxide delivered from a compressed gas cylinder.
(33) FIG. **24**B shows a graph illustrating the pulmonary vascular resistance index (PVRI) of an anesthetized lamb with acute pulmonary hypertension following inhalation of nitric oxide generated using the respiratory system of FIG. **4** with the nitric oxide generator continuously sparking and compared with nitric oxide delivered from a compressed gas cylinder.
(34) FIG. **25**A shows a graph illustrating the mean pulmonary artery pressure (PAP) of an anesthetized lamb with acute pulmonary hypertension following inhalation of nitric oxide generated using the respiratory system of FIG. **4** with the nitric oxide generator intermittently sparking and compared with nitric oxide delivered from a compressed gas cylinder.

(35) FIG. **25**B shows a graph illustrating the pulmonary vascular resistance index (PVRI) of an anesthetized lamb with acute pulmonary hypertension following inhalation of nitric oxide generated using the respiratory system of FIG. **2** with the nitric oxide generator intermittently sparking and compared with nitric oxide delivered from a compressed gas cylinder.

DETAILED DESCRIPTION

(36) The use of the terms “downstream” and “upstream” herein are terms that indicate direction relative to the flow of a gas. The term “downstream” corresponds to the direction of gas flow, while the term “upstream” refers to the direction opposite or against the direction of gas flow.

(37) Currently, administration of inhaled nitric oxide (NO) therapy requires the use of heavy compressed gas cylinders, a gas cylinder distribution network, a complex delivery device, gas monitoring and calibration devices, and trained respiratory therapy staff. These requirements for administering NO therapy present a significant cost to the institution (e.g., a hospital) administering the NO therapy and, therefore, to the patient receiving the NO therapy. For many institutions, inhaled NO therapy can be one of the most expensive drugs used in neonatal medicine. The use of bulky gas cylinders and the expense of inhaled NO therapy result in inhaled NO therapy not being available in most of the world and it is not available for outpatient use.

(38) Several methods have been attempted to produce NO for biomedical purposes, such as, chemically preparing NO from N_2O_4 requiring extensive scavenging with antioxidants. Various electrical systems have also been attempted, such as, pulsed arc, gliding arc, dielectric barrier, microwave, corona, radio frequency induced coupled discharge, and non-thermal atmospheric pressure high-frequency plasma discharge. However, these systems and methods produce large amounts of harmful byproducts (e.g., nitrogen dioxide (NO_2) and ozone (O_3)) and require complex purification systems.

(39) Due to the current difficulties in administering and generating NO for inhalation therapy, it would be desirable to have a lightweight and economical NO generator that can be used for NO inhalation therapy at the bedside of a patient or in portable applications. It would also be desirable to have the NO generator be easily coupled to or integrated into current ventilator systems. It is advantageous from a safety perspective to have the NO that is generated be as clean as possible, so that even in the event that a scavenger fails or is exhausted, the NO that is delivered to a patient is not contaminated with NO_2 or O_3

(40) FIG. **1** shows a respiratory system **10** for administering NO to a patient **11** according to one non-limiting example of the present disclosure. The respiratory system **10** includes a breathing apparatus **12** and a NO generator **14**. In some non-limiting examples, the breathing apparatus **12** can be a ventilator system, a continuous positive airway pressure (CPAP) system, a High Frequency Oscillatory Ventilator (HFOV), a face mask, a nasal cannula or an inhaler. The breathing apparatus **12** is configured to enable the passage of gas to and from an airway of the patient **11**. In some non-limiting examples, the breathing system **12** can provide mechanical ventilation (i.e., positive pressure to inflate the patient's **11** lungs) to the patient. In other non-limiting examples, the patient **11** may be breathing on their own and the breathing system **12** can provide a flow path to the airway of the patient **11**. The illustrated breathing system **12** includes an inspiratory line **18**, an expiratory line **20**, and an airway flowmeter **22** coupled to the inspiratory line **18**. The ventilator **16** can be a commercially available mechanical ventilator used in biomedical applications (e.g., inhalation therapy). As is known in the art, the mechanical ventilator **16** is configured to provide a flow of gas (e.g., air or a nitrogen/oxygen gas mixture) via the inspiratory line **18** to the respiratory tract of the patient **11**. Subsequently, the ventilator **16** is configured to remove a flow of gas (e.g., exhaled gas) via the expiratory line **20** from the respiratory tract of the patient **11**. In this way, the ventilator **16** can simulate the breathing process for the patient **11**. The airway flowmeter **22** measures the flowrate of gas in the inspiratory line **18**. In one non-limiting example, the airway flowmeter **22** may control a timing and amount of NO that is synthesized from spark plasma discharge in the NO generator **14**.

(41) The NO generator **14** is arranged between an inlet **24** and an outlet **26**. Gas (e.g., air or a nitrogen/oxygen gas mixture) is drawn into the NO generator **14** at the inlet **24**. The NO generator **14** is configured to generate a predetermined concentration of NO to be inhaled by the patient **11**, as will be described in detail below. The NO containing gas is furnished from the NO generator **14** to the outlet **26**. The outlet **26** communicates with the inspiratory line **18** of the breathing apparatus **12** upstream of the airway flowmeter **22**.
(42) The respiratory system **10** includes a pre-filter **28**, a gas pump **30**, a gas flow sensor **32** all arranged upstream of the NO generator **14**. The pre-filter **28** is arranged downstream of the inlet **24** and upstream of the gas pump **30**. The gas flow sensor **32** is arranged downstream of the gas pump **30** and upstream of the NO generator **14**. In one non-limiting example, the pre-filter **28** can be configured to filter particles, water droplets and bacteria with a diameter larger than approximately 0.22 micrometers (μm). It should be known that the particle size filtered by the pre-filter **28** is not meant to be limiting in any way, and alternative pre-filters that filter different particle sizes are within the scope of the present disclosure. In other non-limiting examples, the pre-filter **28** may be removed if the fluid provided at the inlet **24** is be pre-treated (i.e., filtered and dried). In some embodiments, a pre-scavenger (not shown) can be arranged upstream of the pre-filter **28** to remove, for example, CO2 from the inlet gas. Removing CO2 from the inlet gas negates the need for the scavenging CO2 in the gas output from the NO generator **14**.
(43) The gas pump **30** is configured to draw gas from inlet **24** and furnish the gas under an increased pressure towards NO generator **14** and through the outlet **26**. It should be known that, in other non-limiting examples, the gas pump **30** can be replaced by a fan or a bellows type device. The gas flow sensor **32** is configured to measure a flowrate of gas flowing from the gas pump **30** to the NO generator **14**. A controller **33** is in communication with the NO generator **14**, the gas pump **30**, the gas flow sensor **32** and the airway flowmeter **22**. The controller **33** is configured to control the operation of the NO generator **14** and the gas pump **30**, as will be described in detail below.
(44) As shown in FIG. **2**, the NO generator **14** includes an oxygen sensor **34** arranged upstream of electrodes **36**. The oxygen sensor **34** measures an oxygen concentration in the gas being supplied, via the gas pump **30**, to the electrodes **36**. In some non-limiting examples, the electrodes **36** can include one or more pairs of individual electrodes that can be fabricated from or plated with tungsten carbide, carbon, nickel, iridium, titanium, platinum, rhenium, or an alloy of the aforementioned materials. In one exemplary non-limiting example, the electrodes **36** are fabricated from or plated with iridium because, as described below, iridium can produce a lower concentration of NO2 relative to the concentration of NO generated which is an important safety factor of the NO generator **14**.
(45) An ignition coil **38** is in communication with the electrodes **36** and is configured to store and release electrical energy. The energy stored by the ignition coil **38** is delivered to the electrodes **36** to create a plasma in a gap between the electrodes **36**. The plasma generated between the electrodes **36** generates NO, as long as nitrogen and oxygen are present in the gas being supplied to the electrodes **36**. The controller **33** is in communication with the ignition coil **38** and is configured to control when the ignition coil **38** delivers the stored energy and, therefore, control when the electrodes **36** spark (i.e., form a plasma and generate NO). It should be known that, in some non-limiting examples, the controller **33** can be combined with the NO generator **14** into a single, portable unit.
(46) Downstream of the electrodes **36**, the NO generator **14** includes a scavenger **42**, a post-filter **44**, a NO sensor **46**, and a NO2 sensor **48**. The post-filter **44** is arranged upstream of the NO and NO2 sensors **46** and **48**, and downstream of the scavenger **42**. The scavenger **42** is configured to remove harmful byproducts (e.g., NO2 and 03) produced in the plasma created by sparking the electrodes **36**. In one non-limiting example, the scavenger **42** can be fabricated from calcium hydroxide (Ca(OH)2). The post-filter **44** is configured to filter particles (e.g., fragments from the scavenger **42** and/or particles that break off from the electrodes **36** during sparking) in the fluid

flowing from the electrodes **36** to the outlet **26**. This can prevent the patient **11** from inhaling particle-laden gas and from inhaling electrode particles that boil off due to high temperatures during sparking. In one non-limiting example, the post-filter **44** can be configured to filter particles with a diameter larger or smaller than approximately 0.22 μm. It should be known that the particle size filtered by the post-filter **44** is not meant to be limiting in any way, and alternative post-filters that filter different particle sizes are within the scope of the present disclosure. However, the particle size filtered by the post-filter **44** should be sufficiently small to maintain the safety and health of the patient **11**.

(47) The NO sensor **46** measures a concentration of NO in the gas flowing from the electrodes **36** to the outlet **26**, and the NO2 sensor **48** measures a concentration of NO2 in the fluid flowing from the electrodes **36** to the outlet **26**.

(48) With continued reference to FIG. **2**, the controller **33** receives input power from a power supply **50**, In one non-limiting example, the power supply **50** can be external to the NO generator **14** (e.g., wall power). In another non-limiting example, the power supply **50** can be integrated into the NO generator **14**. In this non-limiting example, the power supply **50** can be in the form of a battery or a rechargeable battery. The controller **33** includes a transceiver **52** and a communication port **54**. The controller **33** can be configured to communicate wirelessly, via the transceiver **52**, with an external processor (not shown) and/or a display (not shown) using Bluetooth®, WiFi, or any wireless communication protocol known in the art or developed in the future. Alternatively or additionally, the controller **33** can be configured to communicate, via the communication port **54**, with the external processor (not shown) and/or the display (not shown) using a universal serial bus (USB) connection, an Ethernet connection, or any wired communication protocol known in the art or developed in the future.

(49) The controller **33** is in communication with the gas pump **30**, the gas flow sensor **32**, the oxygen sensor **34**, the NO sensor **46** and the NO2 sensor **48**. In operation, the controller **33** is configured to control a displacement (i.e., a flowrate of gas from the inlet **24** to the outlet **26**) of the gas pump **30**. For example, a desired flowrate of 5 liters/minute (L/min) can be input to the controller **33** by the external processor. In this non-limiting example, the controller **33** can adjust the displacement of the gas pump **30** in response to the flowrate measured by the gas flow sensor **32** to attempt to maintain the flowrate within a predefined margin of approximately 5 L/min.

(50) The concentrations measured by the oxygen sensor **34**, the NO sensor **46**, and the NO2 sensor **48** are communicated to the controller **33**. In operation, the controller **33** is configured to vary the timing and the sparking characteristics of the electrodes **36** in response to the measurements of the oxygen sensor **34**, the NO sensor **46** and the NO2 sensor **48** and the airway flowmeter **22**. In one non-limiting example, the timing of the electrodes **36** can be with respect to inspiration of the patient **11**. As shown in FIG. **3**, the controller **33** is configured supply an electrical signal to the ignition coil **38** and thereby to the electrodes **36** that comprises a plurality of square waves. In the non-limiting example shown in FIG. **3**, the electrical signal supplied to the electrodes **36** by the controller **33** can include groups of square waves where each individual square wave in the respective group represents a spark of the electrodes **36**. In this non-limiting example, the controller **33** can be configured to control a number spark groups per second (B), a number of individual sparks per group (N), a time between individual sparks (P), and a pulse duration of each individual square wave in the group (H).

(51) Varying the values of B, N, P, and H can alter concentrations of NO and NO2 generated by the NO generator **14**, as will be described in detail below. The data gathered from varying B, N, P, and H can be used to develop a theoretical model for generating a given concentration of NO. The theoretical model can be further refined by testing the NO generator **14** at different oxygen concentrations, pressures, humidities, and temperatures. Then, knowing the oxygen concentration, pressure, temperature, and/or humidity of the fluid flowing to the electrodes **36**, the controller **33** can calculate an ideal B, N, P, and H to generate a desired concentration of NO. The NO sensor **46**

monitors the concentration of NO produced and provides feedback to the controller **33** which, in response to the concentration of NO produced deviating from a desired concentration, can alter the values of B, N, P, and/or H accordingly.

(52) In one non-limiting example, the oxygen concentration of the gas provided to the electrodes **36** may be a constant, known value (e.g., air with 21% O2) which is input to the controller **33**. In this non-limiting example, the oxygen sensor **34** may be omitted from the NO generator **14**. Alternatively or additionally, a pressure sensor (not shown) can be arranged upstream of the electrodes **36** to measure ambient pressure. As described below, the amount of NO produced by the NO generator **14** can be a function of atmospheric pressure. In one non-limiting example, the controller **33** can be configured to adjust the sparking characteristics of the electrodes **36** in response to the pressure measured by the pressure sensor. Alternatively or additionally, the controller **33** can be configured to monitor a condition, or health, of the scavenger **42** by determining if the concentration of NO2, measured by the NO2 sensor **48**, exceeds a pre-determined value. If the NO2 concentration exceeds the pre-determined value, the scavenger **42** may be exhausted and the controller **33** can cease the sparking of the electrodes **36** and instruct a user of the NO generator **14** to replace the scavenger **42**. Alternatively or additionally, a colorimetric pH sensor can estimate exhaustion of the scavenger **42**.

(53) In operation, the NO generator **14** is configured to produce therapeutic concentrations of NO, for example, between approximately 5 and 80 parts per million (ppm) by pulsed sparking of the electrodes **36**. The therapeutic concentrations of NO produced by the NO generator **14** can be supplied to the inspiratory line **18** and thereby to the patient **11**. Thus, the NO generator **14** does not require the use of valves to enable the flow of NO laden gas to the patient **11**. In one non-limiting example, the electrodes **36** of the NO generator **14** can be triggered, by the controller **33**, to spark continuously. In another non-limiting example, the electrodes **36** of the NO generator **14** can be triggered, by the controller **33**, to spark during or prior to inspiration of the patient **11**. Triggering the electrodes **36** during or prior to inspiration can avoid waste NO generated during exhalation, and can enable the NO generator **14** to demand less power when compared with continuous operation.

(54) The controller **33** can be configured to detect inspiration of the patient **11** based on the flowrate measured by the airway flowmeter **22**, a temperature in the inspiratory line **18**, a temperature in the expiration line **20**, a pressure in the inspiratory line **18**, and/or a pressure in the expiration line **20**. The theoretical model executed by the controller **33** for determining the values of B, N, P, and H for a desired NO concentration can be adjusted whether the electrodes **36** are being sparked continuously or intermittently (i.e., triggered during or prior to inspiration).

(55) FIG. **4** shows a schematic illustration of a respiratory system **100** according to another non-limiting example of the present disclosure. The respiratory system **100** of FIG. **4** is similar to the respiratory system **10** of FIG. **1** except as described below or is apparent from FIG. **4**. As shown in FIG. **4**, the respiratory system **100** includes a NO generator **102** integrated into the inspiratory line **18** of the breathing apparatus **12**. With the NO generator **102** integrated into the inspiratory line **18**, the respiratory system **100** may not include the pre-filter **28**, the gas pump **30**, and the gas flow sensor **32**, as the ventilator **16** provides the flow of gas to the NO generator **102**.

(56) The NO generator **102** of FIG. **5** is similar to the NO generator **14** of FIG. **1** except as described below or is apparent from FIG. **5**. As shown in FIG. **5**, the scavenger **42**, the post-filter **44**, the NO sensor **46** and the NO2 sensor are integrated into the inspiratory line **18**, and the NO generator **102** includes a membrane **104** surrounding or covering the electrodes **36**. The membrane **104** protects the electrodes **36** from any water droplets or mucous in the inspiratory line **18** while allowing the gas flowing through the inspiratory line **18** (e.g., air or a nitrogen/oxygen gas mixture) to freely pass through the membrane **104**. In one non-limiting example, the membrane **104** can be a microporous polytetrafluoroethylene (PTFE) membrane. It should be known that the electrodes **36** do not need be completely integrated into the inspiratory line **18**, and that only the tips of the

electrodes **36** need to be in the gas path defined by the inspiratory line **18**.
(57) In operation, placing the NO generator **102** inline with the inspiratory line **18** reduces the transit time of the generated NO gas to the lung of the patient **11**. This reduces the probability of the generated NO oxidizing to NO2 prior to reaching the patient **11**. Also, placing the NO generator **102** inline with the inspiratory line **18** negates the need for valves to enable the flow of NO laden gas to the patient **11**, In one non-limiting example, the controller **33** is configured to intermittently spark the electrodes **36** of the NO generator **102** prior to or during inspiration of the patient **11**. Generating NO only during or upon inspiration, compared to continuous sparking of the electrodes **36**, enables the NO generator **102** to generate NO during approximately one quarter to one eighth of the total respiratory cycle time of the patient **11**. This can reduce the power demanded of the NO generator **102**, favor portable applications, avoid generating waste NO, and reduce a necessary size of the scavenger **42**.
(58) FIG. **6** shows one non-limiting implementation of the NO generator **102** where the controller **33** and the ignition coil **38** are enclosed in a base **110**. The base **110** is coupled to a tube **112** configured to be placed inline with an inspiratory line of a respiratory system, or breathing apparatus. The electrodes **36** are arranged partially within the base **110** such that the tips of the electrodes **36** are in a fluid path defined by the tube **112**. The illustrated NO generator **102** includes a power cord **114** attached to the base **102** to supply power to the controller **33** and the power supply **50**. The power cord **114** is detachable from the base **110** to aid in the portability of the NO generator **102**.
(59) A first end **116** of the tube **112** is configured to receive a cartridge assembly **118** and a second end **117** of the tube **112** is configured to couple to the inspiratory line **18**. The cartridge assembly **118** includes a cartridge inlet **119** configured to couple to the first end **116** of the tube **112**, a cartridge **120** arranged upstream of and coupled to the post-filter **44**, and a cartridge outlet **122** configured to couple to the inspiratory line **18**. In one non-limiting example, the cartridge **120** can be filled with a microporous material (e.g., foam). The scavenger **42** is arranged between the cartridge **120** and the post-filter **44**.
(60) FIG. **7** shows a respiratory system **200** having an NO generator **201** according to another non-limiting example of the present disclosure. As shown in FIG. **7**, the NO generator **201** includes a chamber **202** having a chamber inlet **204** arranged upstream of electrodes **206**. Similar to the electrodes **36**, described above, the electrodes **206** can be powered by a controller **207** which is configured to control when energy is delivered to the electrodes **206** and, therefore, control when the electrodes **206** spark (i.e., form a plasma and generate NO). The chamber **202** is coupled to a main chamber **208** via passage **210**. The main chamber **208** includes a main inlet **212**, a main outlet **214** and a venturi **216** arranged therebetween. The main outlet **214** is in gas communication with the respiratory tract of a patient. The passage **210** is coupled to the venturi **216** of the main chamber **208** and includes a post-filter **218** and a post-scavenger **220**. The post-filter **218** is configured to filter particles (e.g., particles that break off or are vaporized from the electrodes **36** during sparking) in the gas flowing through the passage **210** from the chamber **202** to the main chamber **208**. The post-scavenger **220** is configured to remove harmful byproducts (e.g., NO2 and O3) produced in the plasma created by sparking the electrodes **206**. In other non-limiting examples, the post-filter **218** and/or the post-scavenger **220** may be arranged in the main chamber **208** downstream of the venturi **216**.
(61) In one non-limiting example, a pre-filter **222** may be arranged upstream of the chamber inlet **202** to remove particles and/or water droplets in the fluid being supplied to the chamber inlet **202**. Alternatively or additionally, a pre-scavenger **224** may be arranged upstream of the chamber inlet **202** to remove compounds which are potentially harmful to the post-scavenger **220** (e.g., carbon dioxide (CO2)). Pre-scavenging the gas flowing to the electrodes **206** can enable a size of the post-scavenger (not the post-filter) **220** to be reduced. Reducing the size of the post-scavenger **220** by pre-scavenging can, in one non-limiting example, enable the post-scavenger **220** to be placed over

a spark gap between the electrodes **206** within a tracheostomy tube or an endotracheal tube to produce NO within the airway, even close to the carina.

(62) One or more sensors **226** are arranged downstream of the venturi **216**, The sensors **226** are configured to measure an oxygen concentration, a NO concentration, and/or an NO2 concentration in the gas flowing from the venturi **216** to the main outlet **214**. Alternatively or additionally, the chamber **202** may include one or more additional sensors (not shown) to measure at least one of a pressure, a temperature, and a humidity in the chamber **202**.

(63) In some non-limiting examples, the main chamber **208**, the chamber **202**, and/or the passage **210** may include one or more other passages or modules, such as a ventilator gas stream or breathing apparatus.

(64) In operation, the main inlet **212** and the chamber inlet. **204** receive a flow of gas (e.g., air or a nitrogen/oxygen gas mixture). The flowrate of gas provided to the main inlet **212** can be sufficiently greater than the flowrate of gas provided to the chamber inlet **204** which causes the flow through the venturi **216** to draw a vacuum on the chamber **202**. The vacuum drawn on the chamber **202** can draw fluid from the chamber **202** into the main chamber **208**. This operation of the NO generator **201** can obviate the need to control the total amount of NO rich gas injected into the main chamber **208** with one or more valves. Also, the NO generator **201** non-mechanically, (i.e., without the use of a pump or valves) provides the flow of NO laden gas to the patient.

(65) The operation of the controller **207** is similar to the controller **33**, described above, and is configured to control the concentration of NO generated by sparking the electrodes **206** by varying B, N, P, and H. The controller **207** can adjust B, N, P, and/or H in response to the measurements by the one or more sensors **226**. In one non-limiting example, the desired concentration of NO generated for a particular application can be calculated by the controller **207** based on the mass flowrate of gas through the main chamber **208** and the amount of vacuum drawn on the chamber **202**. In some non-limiting examples, the NO generator **201** can include a flow sensor (not shown) in communication with the controller **207** to enable timed inspiratory generation of NO. In this non-limiting example, the controller **207** can be configured to trigger the electrodes **206** to generate NO during or prior to inspiration of the patient which can reduce wear of the electrodes **206**, oxidation of NO into NO2, and the power requirements of the NO generator **201**.

(66) FIG. **8** shows a respiratory system **300** having a NO generator **301** according to another non-limiting example of the present disclosure. The NO generator **301** of FIG. **8** is similar to the NO generator **201** of FIG. **7** except as described below or is apparent from FIG. **8**. As shown in FIG. **8**, the NO generator **301** can employ a proportional parallel delivery. Rather than mixing the gas before it is delivered to the patient, an inspiration can pull NO rich gas from the chamber **202** and fluid from the main chamber **208** from a parallel passage **302**. That is, the patient can draw output gas directly from the parallel passage **302** without requiring the use of valves or a pump to furnish the produced NO laden gas to the patient.

(67) As described above, the NO generators **14**, **102**, **201**, and **301** may operate similarly to provide safe and pure NO to a patient's airway. The operation of the respective controller (i.e., controllers **33** and **207**) in the respiratory systems **10**, **100**, **200**, and **300** can control the operation of the NO generators **14**, **102**, **201**, and **301**. FIG. **9** shows one non-limiting example of the operation of any of the above-described respiratory systems **10**, **100**, **200**, and **300**. As shown in FIG. **9**, a NO generator (e.g., NO generator **14**, **102**, **201**, and/or **301**) is coupled to an airway of a patient at step **304**. As described above, the NO generator can be coupled to the airway of the patient, for example via a connection to an inspiration line, a venturi, a parallel path, or the NO generator can be placed inline with an airway of the patient. With the NO generator coupled to the airway of the patient, the controller (e.g., controller **33** or controller **207**) monitors sensor inputs to the patient at step **306**. In some non-limiting examples, the controller can monitor an oxygen concentration downstream of the NO generator, an ambient pressure, a gas flowrate being provided (mechanically or non-mechanically) to the patient, a NO concentration downstream of the NO generator, and a NO2

concentration downstream of the NO generator.
(68) The controller (e.g., controller **33** or controller **207**) then determines at step **308** if the NO generator should be triggered to produce NO to be inhaled by the patient. In some non-limiting examples, the controller can be configured to trigger at or just before an inspiratory event (e.g., by monitoring the gas flow provided to the patient, a pressure in an inspiratory line, a temperatures in an inspiratory line, etc.). In other non-limiting examples, the controller can be manually triggered by a user of the NO generator. Once the NO generator has been triggered by the controller at step **308**, the controller can determine the desired sparking characteristics, provided by a pulsed electrical signal, to be sent to electrodes (e.g., electrodes **36** or electrodes **208**) at step **310**. The controller can be pre-configured to produce a desired concentration of pure and safe NO gas to be inhaled by the patient. In one non-limiting example, the pre-configured concentration of NO gas is determined at step **310** by the controller as a function of the atmospheric pressure and/or the B, N, P, and H electrode spark characteristics, described above. That is, the controller can, based on the measured atmospheric pressure, determine the desired B, N, P, and H of the electrical signal to produce the pre-configured concentration of NO.
(69) With the desired sparking characteristics determined at step **310**, the controller sends the corresponding electrical signal to the electrodes and the NO generator produces, at step **312**, the pre-configured concentration on pure and safe NO gas by spark plasma discharge to be provided to the airway of the patient. While the NO generator is producing NO gas at step **312**, the controller monitors the inputs from the sensors (e.g., an oxygen concentration upstream of the NO generator, an ambient pressure, a gas flowrate being provided (mechanically or non-mechanically) to the patient, a NO concentration downstream of the NO generator, and a NO2 concentration downstream of the NO generator. Based on the inputs from the sensors, the controller determines at step **314** whether or not to adjust the NO production. For example, if controller detects that the output NO gas concentration is not substantially equal to the desired NO gas concentration, the controller can alter the sparking characteristics of the electrodes, at step **316**, by varying at least one of B, N, P, and H to bring the produced NO gas concentration in line with the desired NO gas concentration. Alternatively or additionally, if the controller detects an increase in gas flow being provided to the airway of the patient, the controller can alter the sparking characteristics of the electrodes, at step **316** by varying at least one of B, N, P, and H accordingly. Thus, the controller (e.g., controller **33** or controller **207**) is configured to alter the sparking characteristics (i.e., a concentration of synthesized NO gas produced by spark plasma discharge between the electrodes) based on the feedback from one or more sensors.
EXAMPLES
(70) The following examples set forth, in detail, ways in which the respiratory systems **100** and **200** and/or the NO generators **14**, **102**, **201** and **301** may be used or implemented, and will enable one of skill in the art to more readily understand the principle thereof. The following examples are presented by way of illustration and are not meant to be limiting in any way.
Example 1: Measuring NO and NO2 Generation at Varying Oxygen and Nitrogen Concentrations
(71) The NO generator **14** was tested with varying nitrogen and oxygen concentrations being provided to the electrodes **36**. The test was performed using the test setup shown in FIG. **10** and at atmospheric pressure. The controller **33** was configured to spark the electrodes **36** using the following settings: B=25; N=35; P=240 μs; and H=100 μs. The NO and NO2 concentrations generated by the NO generator **14** were measured at a constant gas flow of 5 L/min and with oxygen levels of 10%, 21%, 50%, 80%, and 90% and a balanced amount of nitrogen. FIG. **11** shows the concentrations of NO and NO2 generated during the test. As shown in FIG. **11**, maximum NO (68±4 ppm) and NO2 (6±2 ppm) concentrations were generated at 50% oxygen. Lower concentrations of NO and NO2 were generated as the oxygen concentration deviated from 50% (i.e., either increasing the oxygen concentration above 50% or decreasing the oxygen concentration below 50%).

Example 2: Measuring the NO and NO2 Concentrations During Continuous Operation for 10 Days
(72) The NO generator **14** was tested at an oxygen concentration of 21% (i.e., in air) and a constant gas flow rate of 5 L/min. The electrodes **36** were fabricated from iridium-platinum. The test was performed using the test setup shown in FIG. **10** and at atmospheric pressure. The controller **33** was configured to spark the electrodes **36** using the following settings to produce approximately 50 ppm of NO: B=20, N=20, P=240 μs; and H=70 μs. FIG. **12** shows the NO and NO2 concentrations generated by the NO generator over the 10 day test. As shown in FIG. **12**, the NO and NO2 concentrations remained substantially constant over the 10 days.
Example 3: Measuring NO and NO2 Generation at Varying B, N, P, and H
(73) As described above, a theoretical model of the NO and NO2 generation at varying B, N, P, and H, can be input to the controller of the respective respiratory system. The NO generator **14** was tested at an oxygen concentration of 21% (i.e., in air) and a constant gas flow rate of 5 L/min. The electrodes were fabricated from iridium-platinum. The test was performed using the test setup shown in FIG. **10** and at atmospheric pressure. FIG. **13**A shows the effect of varying B with N=25, P=240 μs, and H=100 μs. As shown in FIG. **13**A, the NO and NO2 concentrations generated increased substantially and linearly with increasing values of B. FIG. **13**B shows the effect of varying N with B=35, P=240 μs, and H=100 μs. As shown in FIG. **13**B, the NO and NO2 concentrations generated increased substantially and linearly with increasing values of N. FIG. **13**C shows the effect of varying P with B=35, N=25, and H=100 μs. As shown in FIG. **13**C, the NO and NO2 concentrations generated increased substantially and linearly with increasing values of P. FIG. **13**D shows the effect of varying H with B=35, N=25, and P=240 μs. As shown in FIG. **13**D, the NO and NO2 concentration generated increased substantially and linearly with increasing values of H. The data shown in FIGS. **12**A-D indicate that NO production can be precisely controlled (using B, N, P, and H), and that NO production can increase with pulse repetition (B and N) and energy storage capacitance (P and H).
Example 4: Measuring NO and NO2 Generation at Varying Atmospheric Pressure
(74) The NO generator **14** was tested at an oxygen concentration of 21% (i.e., in air) in a 500 milliliter chamber. The controller **33** was configured to spark the electrodes **36** using the following settings: B=100, N=10, P=140 μs; and H=10 μs. The NO generator was run for 1 minute and the NO and NO2 concentrations were measured at one-third atmospheres absolute pressure (ATA), one-half ATA, one ATA, and two ATA. FIG. **14** shows the NO and NO2 concentrations at the varying atmospheric pressures. As shown in FIG. **14**, compared to NO and NO2 concentrations generated at one ATA, the NO and NO2 production decreased with decreasing ATA and increased with increasing ATA. However, the ration of NO2/NO remained substantially constant for each of the atmospheric pressures tested.
Example 5: Measuring NO and NO2 Concentrations Entering and Exiting the Scavenger **42** of the NO Generator **14** at Varying Oxygen and Nitrogen Concentrations
(75) The NO generator **14** was tested at a constant gas flow rate of 5 L/min. The electrodes **36** were fabricated from iridium-platinum. The test was performed using the test setup shown in FIG. **10** at atmospheric pressure. The scavenger **42** comprised 72 grams (g) of Ca(OH)2 and the post-filter **44** was placed downstream of the scavenger **42**. The controller **33** was configured to spark the electrodes **36** using the following settings: B=25, N=35, P=240 μs; and H=100 μs. The NO and NO2 concentrations generated by the NO generator **14** were measured entering (i.e., upstream) and exiting (i.e., downstream) of the scavenger **42** at oxygen levels of 21% (i.e., air), 50%, and 80%, and a balanced amount of nitrogen. FIG. **15** shows the concentrations of NO and NO2 measured during the test. As shown in FIG. **15**, at 21% oxygen (i.e., in air), the NO generator **14** produced 48±5 ppm NO and 44±5 ppm exited the scavenger **42**. The NO generator **14** produced 4.1±0.4 ppm NO2 and 0.5±0.03 ppm exited the scavenger **42**. At 50% oxygen, the NO generator **14** produced 68±11 ppm NO and 62±11 ppm exited the scavenger **42**. The NO generator **14** produced 6.2±0.4 ppm NO2 and 0.7±0.02 ppm exited the scavenger **42**. At 80% oxygen, the NO generator **14**

produced 41±1 ppm NO and 37±2 ppm exited the scavenger **42**. The NO generator **14** produced 3.9±0.5 ppm NO2 and 0.9±0.04 ppm exited the scavenger **42**. Thus, the scavenger **42** removed between approximately 87% and 95% of the NO2 produced by the NO generator **14**. These results demonstrate that the scavenger **42** is highly efficient at removing NO2 (to below the Environmental Protection Agency (EPA) limit after scavenging) without reducing the NO concentrations.

Example 6: Measuring NO and NO2 Concentrations Entering and Exiting the Scavenger **42** of the NO Generator **102**

(76) As described above, the NO generator **102** is similar to the NO generator **14** but is arranged inline on the inspiratory line **18**, upstream of exhaled CO2, which enables the scavenger **42** to be of a reduced size. The NO generator **102** was tested at a constant gas flow rate of 5 L/min. The test was performed using the test setup shown in FIG. **10** at atmospheric pressure. The electrodes **36** were fabricated from iridium-platinum. The scavenger **42** comprised 15 g of Ca(OH)2 and the post-filter **44** was placed downstream of the scavenger **42**. The controller **33** was configured to spark the electrodes **36** using the following settings: B=35, N=25, P=240 μs; and H=70 μs. The NO and NO2 concentrations generated by the NO generator **102** were measured entering (i.e., upstream) and exiting (i.e., downstream) the scavenger **42** at oxygen levels of 21% (i.e., air), 50%, and 80%, and a balanced amount of nitrogen. FIG. **16** shows the concentrations of NO and NO2 measured during the test. As shown in FIG. **16**, the scavenger **42** removed approximately over 95% of the NO2 produced by the NO generator **102**. These results are similar to the larger (75 g) scavenger **42**. Thus, the smaller scavenger **42** with less gas flow resistance (e.g., 0.2 cmH20*min*L−1), used in the NO generator **102**, efficiently removes NO2 without reducing the NO concentrations.

Example 7: Measuring and Scavenging O3 Concentrations Produced by the NO Generator **14**

(77) The NO generator **14** was tested at a constant gas flow rate of 5 L/min. The electrodes **36** were fabricated from iridium-platinum. The test was performed using the test setup shown in FIG. **10** and at atmospheric pressure. The scavenger **42** comprised 72 grams (g) of Ca(OH)2 and the post-filter **44** was placed downstream of the scavenger **42**. The controller **33** was configured to spark the electrodes **36** using the following settings: B=25, N=35, P=240 μs; and H=100 μs. The O3 concentrations generated by the NO generator **14** were measured entering (i.e., upstream) and exiting (i.e., downstream) of the scavenger **42** at oxygen levels of 21% (i.e., air), 50%, and 80%, and a balanced amount of nitrogen. FIG. **17** shows the concentrations of O3 measured during the test. As shown in FIG. **17**, at 21% oxygen (i.e., in air), the NO generator **14** produced 17±2 parts per billion (ppb) O3 and <0.1 ppb exited the scavenger **42**. At 50% oxygen, the NO generator **14** produced 18±10 ppb O3 and <0.1 ppb exited the scavenger **42**. At 80% oxygen, the NO generator **14** produced 20±1 ppb O3 and <0.1 ppb exited the scavenger **42**. These results demonstrate that the scavenger **42** is highly efficient at removing O3 to negligible levels well below the EPA O3 limits. Similar results were achieved when testing of the smaller scavenger **42** of the NO generator **102**.

Example 8: Electrode Erosion

(78) As described above, the electrodes can break down and vaporize over time due to the sparking. FIG. **18**A shows a new iridium electrode tip and FIG. **18**B shows a used iridium electrode tip after ten days of operation producing 50 ppm NO at 5 L/min gas flowrate. As shown in FIG. **18**B, the electrode tip has degraded and lost material due to the sparking events. Thus, the requirement for the post-filter **44** in the NO generator **14** and **102**, and the post-filter **218** in the NO generator **201** and **301**. As the electrodes erode and vaporize, the electrode fragments are deposited on the post-filter **44**, **218**. To verify that the post-filter **44**, **218** catches the electrode fragments, a post-filter with a 0.22 μm particle size cutoff was imaged after the ten days of sparking. FIG. **19**A shows a new 0.22 μm post-filter and FIG. **19**B shows the 0.22 μm post-filter after the ten days of operation. As shown in FIG. **19**B, the used 0.22 μm post-filter contains iridium fragments. This was verified by energy-dispersive X-ray (EDX) spectroscopy as shown in the plots of FIG. **20**A and FIG. **20**B. FIG. **20**A shows the EDX spectroscopy of the new 0.22 μm post-filter and FIG. **20**B shows the EDX spectroscopy of the used 0.22 μm post-filter. As shown in FIGS. **20**A and **20**B, the used 0.22

μm post-filter contains iridium while the new 0.22 μm post-filter does not contain iridium. Thus, a single 0.22 μm post-filter was sufficient and necessary to catch electrode fragments produced by electrode erosion.

Example 9: Minimizing NO2 Generation by Varying Electrode Composition

(79) The NO generator **14** was tested at a constant gas flow rate of 5 L/min with electrodes **36** fabricated from tungsten carbide, carbon, nickel, and iridium. The test was performed using the test setup shown in FIG. **10** and at atmospheric pressure. The controller **33** was configured to spark the electrodes **36** using the following settings: B=25, N=35, P=240μs; and H=50 μs. FIG. **21** shows the ratio of NO2/NO generated for the different electrode compositions. As shown in FIG. **21**, the iridium electrode produced 4.5±0.1% of NO2/NO, the nickel electrode produced 6.5±0.1% of NO2/NO, the carbon electrode produced 7.8±0.5% of NO2/NO, and the tungsten carbide electrode generated 12.9±1.9% of NO2/NO. Obviously, the lower the ratio of NO2/NO the better and, thus, the iridium electrode is an ideal candidate for the composition of the electrodes **36**.

Example 10: Measuring NO and NO2 Diffusion Rates Through the Membrane **104** of the NO Generator **102**

(80) As described above, since the NO generator **102** is placed inline with the inspiratory line **18**, the microporous membrane **104** can be placed around the electrodes **36** to protect them from droplets of water or airway secretions. The NO generator **102** was tested at a constant gas flow rate of 0.5 L/min for 5 minutes while producing NO. The NO and NO2 produced was averaged over the 5 minutes and the concentrations with (+) and without (−) the membrane **104** were measured. The controller **33** was configured to spark the electrodes **36** using the following two sets of settings. Setting #1: B=25, N=35, P=240 μs; and H=30 μs. Setting #2: B=25, N=35, P=240 μs; and H=60μs. FIG. **22** shows the NO and NO2 concentrations produced during the 5 minutes with (+) and without (−) the membrane **104** at the two different spark settings. As shown in FIG. **22**, **95**±2% of the NO generated without (−) the membrane **104** was generated with (+) the membrane **104**, and 95±1% of the NO2 generated without (−) the membrane **104** was generated with (±) the membrane **104**. Thus, the addition of the membrane **104** does not significantly alter the NO production characteristics of the NO generator **102**.

(81) Animal Studies

(82) Animal studies were approved by the Institutional Animal Care and Use Committee of Massachusetts General Hospital (Boston, MA). Eight lambs (New England Ovis, Dover, NH) weighing 32±2 kg were studied. General anesthesia was induced with 5% inhaled isoflurane (1-chloro-2,2,2-trifluoroethyldifluromethyl ether, Baxter, Deerfield, IL) in oxygen delivered via a mask and then maintained with 1-4% isoflurane in 50% oxygen during surgery. After tracheal intubation, the lambs were instrumented with indwelling carotid artery pulmonary artery catheters. All hemodynamic measurements were performed in anesthetized lambs ventilated with a mechanical ventilator (model 7200, Puritan Bennett, Pleasanton, CA) at a tidal volume of 400 ml/min and rate of 12-15 breaths/min.

(83) To induce pulmonary hypertension, a potent pulmonary vasoconstrictor U46619 (Cayman Chemical, Ann Arbor, MI), the analog of the endoperoxide prostaglandin H2, was infused intravenously at a rate of 0.8-0.9 μg/kg/min to increase pulmonary arterial pressure (PAP) to 30 mmHg. The mean arterial pressure and PAP were continuously monitored using a Gould 6600 amplifier system (Gould Electronics, Inc., Eastlake, OH). Pulmonary capillary wedge pressure, heart rate, and cardiac output were intermittently measured at baseline, during U46619 infusion, and before and after inhalation of NO generated using either the respiratory system **10**, the respiratory system **100**, or NO delivered and diluted at the same level from a compressed gas cylinder. Cardiac output was assessed by thermal dilution as the average of three measurements after an intravenous bolus injection of 10 mL of ice-cold saline solution. Pulmonary vascular resistance index (PVRI), as well as cardiac index (CI), were calculated using standard formulae. The gas cylinder contained 500 ppm NO diluted in nitrogen.

Example 1.1: Continuous NO Generation from Air Using the Respiratory System **10** on Anesthetized Lambs

(84) The respiratory system **10** was tested with an anesthetized lamb as the patient **11**. A baseline (BL) was generated then the NO generator **14** of the respiratory system **10** was triggered to continuously spark (i.e., generate NO) after 1746619 was administered for 30 minutes. The NO was pumped at 5 L/min into the inspiratory line **18**. The electrodes **36** were fabricated from iridium-platinum. Once triggered, the controller **33** was configured to spark the electrodes **36** for 4 minutes using the following settings: B=35, N=25, P=240 μs; and H=100 μs, which produced approximately 40 ppm of NO, and then the controller **33** stopped the NO generator **14**. The test was performed when 21% oxygen was supplied to the inlet **24** of the NO generator **14**, when 50% oxygen was supplied to the inlet **24** of the NO generator **14**, and compared with NO supplied at the same concentration to the anesthetized lamb from a gas cylinder.

(85) FIG. **23**A shows the mean pulmonary artery pressure (PAP) of the anesthetized lamb for the duration of the tests, and FIG. **23**B shows the pulmonary vascular resistance index (PVRI) of the anesthetized lamb for the duration of the tests. As shown in FIGS. **23**A and **23**B, during the 4 minute window **400** when NO was continuously produced by the NO generator **14**, PAP and PVRI were rapidly reduced while breathing both 21% and 50% oxygen. Also, the reduction in PAP and PVRI for the NO produced by the NO generator **14** was similar to the reduction in PAP and PVRI for the NO supplied at the same level by dilution from the gas cylinder. Therefore, the respiratory system **10** can be a viable and equivalent replacement for gas cylinders when administering NO inhalation therapy.

Example 12: Continuous NO Generation from Air Using the Respiratory System **100** on Anesthetized Lambs

(86) The respiratory system **100** was tested with an anesthetized lamb as the patient **11**. A baseline (BL) was generated then the NO generator **102** of the respiratory system **100** was triggered to continuously spark (i.e., generate NO) after U46619 was administered for 30 minutes. The electrodes **36** were fabricated from iridium-platinum. Once triggered, the controller **33** was configured to spark the electrodes **36** for 4 minutes using the following settings: B=35, N=25, P=240 μs; and H=100 μs, which produced approximately 40 ppm of NO, and then the controller **33** stopped the NO generator **102**. The test was performed when 21% oxygen was supplied in the inspiratory line **18**, when 50% oxygen was supplied in the inspiratory line **18**, and when NO was supplied to the anesthetized lamb diluted from a compressed gas cylinder.

(87) FIG. **24**A shows the mean pulmonary artery pressure (PAP) of the anesthetized lamb for the duration of the tests, and FIG. **24**B shows the pulmonary vascular resistance index (PVRI) of the anesthetized lamb for the duration of the tests. As shown in FIGS. **24**A and **24**B, during the 4 minute window **402** when NO was continuously produced by the NO generator **102**, PAP and PVRI were rapidly reduced while breathing both 21% and 50% oxygen. Also, the reduction in PAP and PVRI for the NO produced by the NO generator **102** was similar to the reduction in PAP and PVRI for the NO supplied by the gas cylinder. Also, the performance of the respiratory system **100** was similar to the respiratory system **10**. Therefore, the respiratory system **100** can provide a viable and equivalent replacement for compressed gas cylinders when administering NO inhalation therapy.

Example 13: Intermittent NO Generation from Air Using the Respiratory System **100** on Anesthetized Lambs

(88) The respiratory system **100** was tested with an anesthetized lamb as the patient **11**. A baseline (BL) was generated then the NO generator **102** of the respiratory system **100** was triggered to intermittently spark (i.e., generate NO) after U46619 was administered for 30 minutes. The electrodes **36** were fabricated from iridium-platinum. The controller **33** was configured to spark the electrodes **36** only during the first 0.8 seconds of inspiration for 4 minutes using the following settings: B=35, N=25, P=240 μs; and H=100 μs and then the controller **33** stopped the NO generator **102**, The test was performed when 21% oxygen was supplied in the inspiratory line **18**,

when 50% oxygen was supplied in the inspiratory line **18**, and when NO was supplied to the anesthetized lamb from a gas cylinder.

(89) FIG. **25**A shows the PAP of the anesthetized lamb for the duration of the tests, and FIG. **25**B shows the PVRI of the anesthetized lamb for the duration of the tests. As shown in FIGS. **24**A and **24**B, during the 4 minute window **404** when NO was produced during the first 0.8 seconds of inspiration by the NO generator **102**, mean pulmonary artery pressure (PAP) and the pulmonary vascular resistance index (PVRI) were rapidly reduced breathing either 21% and 50% oxygen. Also, the reduction in PAP and PVRI for the NO produced by the NO generator **102** was similar to the reduction in PAP and PVRI for NO supplied and diluted from the compressed gas cylinder. Also, the performance of the respiratory system **100** when intermittently sparking the electrodes **36** was similar to the respiratory system **100** and the respiratory system **10** when continuously sparking the electrodes **36**. Therefore, intermittently generating NO with the respiratory system **100** can be a viable replacement for gas cylinders when administering NO inhalation therapy.

(90) Whilst the invention has been described above, it extends to any inventive combination of features set out above or in the following description. Although illustrative embodiments of the invention are described in detail herein with reference to the accompanying drawings, it is to be understood that the invention is not limited to these precise embodiments. Furthermore, it is contemplated that a particular feature described either individually or as part of an embodiment can be combined with other individually described features, or parts of other embodiments, even if the other features and embodiments make no mention of the particular feature. Thus, the invention extends to such specific combinations not already described.

(91) While the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. The entire disclosure of each patent and publication cited herein is incorporated by reference, as if each such patent or publication were individually incorporated by reference herein.

Claims

1. An apparatus for generating nitric oxide comprising: one or more pairs of electrodes configured to generate a gas comprising nitric oxide from a fluid flowing to the one or more pairs of electrodes; one or more sensors configured to measure at least one of a pressure, a temperature, and a humidity of the fluid flowing to the one or more pairs of electrodes; and a controller in communication with the one or more pairs of electrodes and the one or more sensors and configured to supply an electrical signal to the electrodes that controls timing and sparking characteristics of the one or more pairs of electrodes to produce a concentration of nitric oxide generated by the one or more pairs of electrodes, the controller being configured to determine the timing and sparking characteristics based on measurements from the one or more sensors to generate a desired concentration of NO, wherein the controller is configured to determine the timing and sparking characteristics by controlling a value of one or more of a number of spark groups per second (B), a number of individual sparks per group (N), a time between individual sparks (P), and a pulse duration of each individual wave in the spark group (H) based on the measurements from the one or more sensors, wherein the controller is configured to calculate the value of the one or more of the B, N, P, and H using a model for generating the desired concentration of NO using the measurements from the one or more sensors.

2. The apparatus of claim 1, wherein the controller is configured to calculate the value of the one or more of the B, N, P, and H based on at least one of the pressure, the temperature, and the humidity of the fluid flowing to the electrodes using information from the one or more sensors.

3. The apparatus of claim 1, further comprising an NO sensor configured to measure the

concentration of NO in the gas flowing from the one or more electrodes, and wherein the NO sensor provides feedback to the controller such that the controller is configured to alter the values of at least one of B, N, P, and H in response to the concentration of NO measured by the NO sensor deviating from the desired concentration of NO.

4. The apparatus of claim 1, further comprising an ignition coil in communication with the controller and the one or more electrodes.

5. The apparatus of claim 4, wherein the controller is configured to instruct the ignition coil to supply stored electrical energy to the one or more electrodes.

6. The apparatus of claim 1, further comprising an inspiration sensor configured to provide an indication of inspiration.

7. The apparatus of claim 6, wherein the controller is configured to supply the electrical signal to the one or more electrodes in response to detecting inspiration.

8. The apparatus of claim 1, wherein the desired concentration of NO is between approximately 5 and 80 parts per million.

9. An apparatus for generating nitric oxide comprising: one or more pairs of electrodes configured to generate a gas comprising nitric oxide from a fluid flowing to the one or more pairs of electrodes; one or more sensors configured to measure at least one of a pressure, a temperature, and a humidity of the fluid flowing to the one or more pairs of electrodes; and a controller in communication with the one or more pairs of electrodes and the one or more sensors and configured to supply an electrical signal to the electrodes that controls timing and sparking characteristics of the one or more pairs of electrodes to produce a concentration of nitric oxide generated by the one or more pairs of electrodes, the controller being configured to control the concentration of nitric oxide generated by the one or more pairs of electrodes by controlling one or more of a number of spark groups per second (B), a number of individual sparks per group (N), a time between individual sparks (P), and a pulse duration of each individual wave in the spark group (H) based on the measurements from the one or more sensors, wherein the controller is configured to calculate the B, N, P, and H using a model for generating a desired concentration of NO with measurements from the one or more sensors.

10. The apparatus of claim 9, wherein the controller is configured to calculate B, N, P, and H based on at least one of the pressure, the temperature, and the humidity of the fluid flowing to the electrodes using information from the one or more sensors.

11. The apparatus of claim 9, wherein the desired concentration of NO is between approximately 5 and 80 parts per million.

12. The apparatus of claim 9, wherein the one or more sensors includes a pressure sensor arranged upstream of the one or more electrodes to measure ambient pressure.

13. The apparatus of claim 9, further comprising an NO sensor configured to measure the concentration of NO in the gas flowing from the one or more electrodes.

14. The apparatus of claim 13, wherein the NO sensor provides feedback to the controller such that the controller is configured to alter the values of at least one of B, N, P, and H in response to the concentration of NO measured by the NO sensor deviating from a desired concentration of NO.

15. The apparatus of claim 9, further comprising an ignition coil in communication with the controller and the one or more electrodes.

16. The apparatus of claim 15, wherein the controller is configured to instruct the ignition coil to supply stored electrical energy to the one or more electrodes.

17. The apparatus of claim 9, further comprising an inspiration sensor configured to provide an indication of inspiration.

18. The apparatus of claim 17, wherein the controller is configured to supply the electrical signal to the one or more electrodes in response to detecting inspiration.