(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 December 2016 (01.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/191506 A1

(51) International Patent Classification:
A61B 5/1455 (2006.01) *A61M 16/16* (2006.01)
A61M 16/10 (2006.01)

(21) International Application Number:
PCT/US2016/034198

(22) International Filing Date:
25 May 2016 (25.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/166,116 25 May 2015 (25.05.2015) US

(71) Applicant: **GENO LLC** [US/US]; 2941 Oxbow Circle, Cocoa, FL 32926 (US).

(72) Inventors: **TECTOR, Alfred**; 9170 North Range Line Road, Milwaukee, WI 53217 (US). **PETIT, Priscilla, C.**; 2199 Corner Point Court, Orlando, FL 32820 (US). **DASSE, Kurt, A.**; 213 Garden Street, Needham, MA 02492 (US). **FINE, David, H.**; 2941 Oxbow Circle, Cocoa Beach, FL 32926 (US).

(74) Agents: **FOX, Harold, H.** et al.; Steptoe & Johnson LLP, 1330 Connecticut Avenue, NW, Washington, DC 20036 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: NITRIC OXIDE TREATMENT SYSTEM AND METHOD

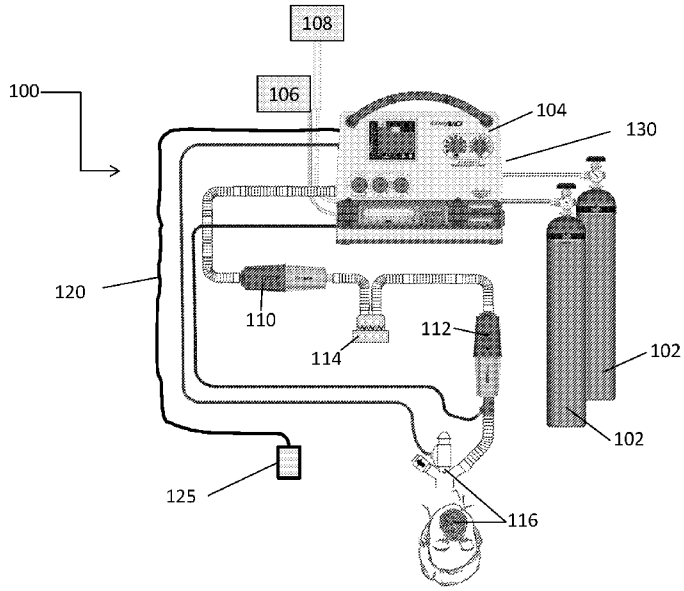


FIG. 1

(57) Abstract: Various systems generating nitric oxide are disclosed herein. According to one embodiment, the system includes a first gas source providing nitrogen dioxide mixed in air or oxygen, and a second gas source supplying compressed air and/or compressed oxygen. The system also includes a ventilator coupled to the first and second gas sources, wherein the ventilator is resistant to nitrogen dioxide. The ventilator regulates gas flow and allows for the adjustment of nitrogen dioxide concentration in the gas flow. The system further includes one or more conversion devices operably coupled to the ventilator where the conversion devices convert nitrogen dioxide into nitric oxide. A patient interface delivers nitric oxide to the patient and is operably coupled to the conversion devices. The system allows oxygen and nitric oxide levels to be varied independently.

WO 2016/191506 A1

NITRIC OXIDE TREATMENT SYSTEM AND METHOD

PRIORITY CLAIM

This application claims priority to U.S. Provisional Application No. 62/166,116, filed May 25, 2015, which is incorporated byt reference in its entirety.

TECHNICAL FIELD

The invention relates to systems and methods for the nitric oxide treatment.

BACKGROUND

Nitric oxide (NO), also known as nitrosyl radical, is a free radical that is an important signaling molecule. For example, NO causes smooth muscles in blood vessels to relax, thereby resulting in vasodilation and increased blood flow through the blood vessel. These effects are limited to small biological regions since NO is highly reactive with a lifetime of a few seconds and is quickly metabolized in the body.

Typically, NO gas is supplied in a bottled gaseous form diluted in nitrogen gas (N_2). Great care has to be taken to prevent the presence of even trace amounts of oxygen (O_2) in the tank of NO gas because NO, in the presence of O2, is oxidized into nitrogen dioxide (NO_2). Unlike NO, the part per million levels of NO_2 gas is highly toxic if inhaled and can form nitric and nitrous acid in the lungs.

SUMMARY

In general, a system for delivering nitric oxide to a patient can include a patient monitor configured to monitor blood oxygen level in the patient, a gas source to provides a gas flow having a dosage amount of nitrogen dioxide based on the monitored blood oxygen level in the patient, one or more conversion devices operably coupled to the gas source, wherein the conversion devices convert nitrogen dioxide into nitric oxide, and a patient interface operably coupled to the conversion devices, wherein the patient interface delivers the dosage amount of the nitric oxide to the patient.

In certain embodiments, the gas source can include a ventilator.

In certain embodiments, the patient monitor can include an oxygen pulse oximeter.

In certain embodiments, the system can include a feedback controller that regulates the nitric oxide dose based on a reading from the oxygen pulse oximeter.

In another aspect, a method for delivering nitric oxide to a patient can include monitoring blood oxygen level in the patient, providing a dosage amount of nitrogen dioxide based on the monitored blood oxygen level in the patient, converting the nitrogen dioxide into nitric oxide and supplying the dosage amount of the nitric oxide to the patient.

According to one embodiment, the system can include a first gas source providing nitrogen dioxide mixed in air or oxygen, and a second gas source supplying compressed air and/or compressed oxygen. The system can also include a ventilator coupled to the first and second gas sources, wherein the ventilator is resistant to nitrogen dioxide. The ventilator regulates gas flow and allows for the adjustment of nitrogen dioxide concentration in the gas flow. The system further includes one or more conversion devices operably coupled to the ventilator where the conversion devices convert nitrogen dioxide into nitric oxide. A patient interface delivers nitric oxide to the patient and is operably coupled to the conversion devices.

In another embodiment, the system includes a humidifier that is placed prior to the first conversion device. In yet another embodiment, the humidifier is integral with the conversion device. Optionally, the system includes an active humidifier that is placed prior to a second conversion cartridge which is adjacent to the patient interface.

The system allows oxygen and nitric oxide levels to be varied independently. The system also includes safeguards in the event of system failure. In one embodiment, the main conversion cartridge in the system is designed to have sufficient capacity to convert the entire contents of more than one bottle of nitrogen dioxide in the event of system failure. In another embodiment, a second conversion cartridge is also included as a redundant safety measure where the second conversion cartridge is able to convert the entire contents of a bottle of nitrogen dioxide into nitric oxide.

Other features will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate by way of example, the features of the various embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of one embodiment of a nitric oxide (NO) generating system.

FIG. 2 is a block diagram of one embodiment of a NO generating system.

FIG. 3 is a perspective view of one embodiment of a system for delivering NO to a patient.

FIG. 4 is a cross-sectional view of one embodiment of a NO generating device.

FIG. 5 is a block diagram of another embodiment of a NO generating device.

DETAILED DESCRIPTION

Various systems and devices for generating nitric oxide (NO) are disclosed herein. Generally, NO is inhaled or otherwise delivered to a patient's lungs. Since NO is inhaled, much higher local doses can be achieved without concomitant vasodilation of the other blood vessels in the body. Accordingly, NO gas having a concentration of approximately 0.5 to approximately 1000 ppm (e.g., greater than 0.5, 1, 2, 3, 4, 5, 10, 12, 14, 16, 18, 20, 30, 40, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1400, 1600, 1800 and 2000 ppm) may be delivered to a patient. Accordingly, doses of NO may be used to prevent, reverse, or limit the progression of disorders which can include, but are not limited to, pulmonary arterial hypertension, idiopathic pulmonary fibrosis, acute pulmonary vasoconstriction, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of a newborn, perinatal aspiration syndrome, haline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia. NO can also be used to treat chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension, or chronic hypoxia.

Currently, approved devices and methods for delivering inhaled NO gas require complex and heavy equipment, and they are limited in their output to 80 ppm of NO because of the presence of the toxic compound, nitrogen dioxide (NO_2). NO gas is stored in heavy gas bottles with nitrogen and no traces of oxygen. NO gas is mixed with air or oxygen with specialized injectors and complex ventilators, and the mixing process is monitored with equipment having sensitive microprocessors and electronics. All this equipment is required in order to ensure that NO is not oxidized into NO_2 during the mixing process since NO_2 is highly toxic. However, this equipment is not conducive to use in routine hospital and non-medical facility settings since the size, cost, complexity, and safety issues restrict the operation of this equipment to highly-trained professionals who are specially trained in its use.

FIGS. 1-2 illustrate one embodiment of a system 100 that generates NO from NO_2. Importantly, patient monitor 120 is configured to monitor the blood oxygen level in the

patient. Monitor 120 can be connected to sensor 125, which can be, for example, a pulse oximetry sensor. The gas source 102 is configured to provide a gas flow having a dosage amount of nitrogen dioxide based on the monitored blood oxygen level in the patient. The dosage amount of nitrogen dioxide is converted to the same dosage amount of nitric oxide prior to delivery to the patient, for example, through use of a feedback controller 130. By using an oxygen pulse oximeter to control the nitric oxide dose to the patient, poor blood oxygen levels can be readily addressed during nitric oxide treatment. Once the instrument is set up and delivering nitric oxide, the dose can be controlled by the pulse oximeter to provide a constant oxygen blood oxygen level. The patients who can benefit from this control can be those that are hypoxic, for example, those suffering from PAH or IPF-PH, plus many others. Instead of delivering fixed amounts of nitric oxide and then weaning the patient, the monitoring of blood oxygen can dictate what the nitric oxide dose needs to be with a feedback control algorithm.

The system 100 may be used in a medical setting such as, but not limited to, an operating theatre or an intensive care unit. The system 100 includes a gas source 102 containing NO_2 premixed in air or oxygen. As shown in FIG. 1, the system 100 includes two gas sources 102 where one bottle is a standby in the event the first bottle becomes depleted. Alternatively, the system 100 may include a single gas source capable of producing NO. In another embodiment, the system 100 may include a plurality of gas sources capable of producing NO. Optionally, if more than one gas source is provided with the system 100, a valve (not shown) is coupled to the gas sources and allows for switching between the gas sources.

The system 100 includes a ventilator 104 connected to the gas sources 102 capable of producing NO in addition to a gas source of compressed air 106 and oxygen 108, as shown in FIG. 1. The ventilator 104 also includes components such as mixing valves (not shown) that are resistant to NO_2 gas. In one embodiment, the mixing valves (not shown) used in the ventilator 102 are manufactured by Bio-Med Devices of Guilford, Connecticut. The ventilator 104 is also provided with controls to independently vary the concentration of NO_2 and oxygen. Accordingly, the mixing valves and the ventilator 104 regulate and adjust the concentration of the gas so that it is at a proper concentration to be converted into a therapeutic dose of NO at the main conversion cartridge 110. Additionally, the ventilator 104 can be adjusted to provide the proper gas flow pattern.

As shown in FIGS. 1-2, the gas passes through the main conversion cartridge 110 where NO_2 in the gas flow is converted to NO. In one embodiment, a passive humidifier

(not shown) is positioned to the main cartridge 110. The passive humidifier operates at a dew point of approximately less than 18°C (not shown) that may be separate or integral with the main cartridge 110. The NO gas generated by the main conversion cartridge 110 then flows through an active humidifier 114, which provides moisture to the patient and also extends the lifespan of the conversion cartridge 112. The humidified NO gas then filters through a secondary cartridge 112 (also referred to as a recuperator) to convert any NO_2 in the gas lines into NO. The NO gas (in air or oxygen) is then delivered to a patient via a patient interface 116. The patient interface 116 may be a mouth piece, nasal cannula, face mask, or fully-sealed face mask. The active humidifier brings the moisture content of the NO gas (and air/oxygen) up to a dew point of approximately 32 to 37°C, thereby preventing moisture loss from the lungs.

As shown in FIGS. 1-2, a single humidifier 114 is positioned between the conversion cartridges 110, 112. In another embodiment, the system 100 may include humidifiers 114 placed prior to each conversion cartridge 110, 112. As shown in FIGS. 1-2, the humidifier 114 is a separate device, but it is contemplated that the humidifier may be an integral component of each conversion cartridge (not shown). According to one embodiment, the humidifier 114 used in the system 100 is manufactured by Fisher and Pykell.

Additionally, the system 100 may include one or more safety features. In one embodiment, the main conversion cartridge 110 is sized so that it has excess capacity to convert NO_2 into NO. For example, the main conversion cartridge 110 is sized to convert the entire contents of more than one gas bottle 102 of NO_2 gas. If the main conversion cartridge 110 were to fail, the recuperator cartridge 112 has sufficient capacity to convert the entire contents of a gas bottle 102. In yet another embodiment, NO_2 and the NO gas concentrations may be monitored after the main conversion cartridge 110. In one embodiment, the gas concentrations of NO and NO_2 may be monitored by one or more NO and N02 detectors manufactured by Cardinal Healthcare, Viasys Division. If any NO_2 is detected, visual and/or auditory alarms would be presented to the operator. The alarms will allow the operator to correct the problem, but the recuperator cartridge 112 would convert any NO_2 that was present in the gas lines back into NO. This function is important at very high NO levels (>40 ppm) as well as during start up of the system 100. Additionally, the recuperator cartridge 112 makes it unnecessary to flush the lines to remove NO_2, since the NO_2 in the lines would be converted to NO by the recuperator prior to delivery to a patient.

FIG. 3 illustrates another embodiment of a system 300 for delivering NO to a patient. The system 300 is provided on a wheeled stand 302. The system 300 includes a ventilator 102 that is resistant to NO_2gas. The system 300 also includes two gas sources 102 for providing NO_2 gas. Additionally, a third gas source 306 is also mounted in the center of the stand 302. The third gas source 306 contains NO_2 in air or oxygen at an appropriate concentration. The third gas source 306 is also connected to the ventilator 102 by gas plumbing and is in a standby mode. In the event of a disruption of the NO_2 gas, compressed air, or compressed oxygen, an automatic series of valves would shut down the feed of gas to the ventilator 104 and replace it with gas from the back up gas source 306. This safety feature is on standby mode and may be implemented within the time frame of a single breath. If the ventilator 104 malfunctions, the third gas source 306 is available as substitute for the system 300. The third gas source 306 includes a NO conversion cartridge 308 and may be used to deliver NO to the patient by means of a handheld ventilator (not shown).

Conversion Cartridges

FIG. 4 illustrates one embodiment of a device 400 that generates NO from NO_2. The device 100, which may be referred to as a NO generation cartridge, a GENO cartridge, a GENO cylinder, or a recuperator, includes a body 402 having an inlet 404 and an outlet 406. The inlet 404 and outlet 406 are sized to engage gas plumbing lines or directly couple to other components such as, but not limited to, gas tanks, regulators, valves, humidifiers, patient interfaces, or recuperators. Additionally, the inlet 404 and outlet 406 may include threads or specially designed fittings to engage these components.

As shown in FIG. 4, the body 402 is generally cylindrical in shape and defines a cavity that holds a porous solid matrix 408. According to one embodiment, the porous solid matrix 408 is a mixture of a surface-activated material such as, but not limited to, silica gel and one or more suitable thermoplastic resins. The thermoplastic resin, when cured, provides a rigid structure to support the surface-activated material. Additionally, the porous thermoplastic resin may be shaped or molded into any form.

According to one embodiment, the porous solid matrix 408 is composed of at least 20% silica gel. In another embodiment, the porous solid matrix 408 includes approximately 20% to approximately 60% silica gel. In yet another embodiment, the porous solid matrix 408 is composed of 50% silica gel. As those skilled in the art will appreciate, any ratio of silica gel to thermoplastic resin is contemplated so long as the mechanical and structural strength of the porous solid matrix 408 is maintained. In one embodiment, the densities of

the silica gel and the thermoplastic resin are generally similar in order to achieve a uniform mixture and, ultimately, a uniform porous solid matrix 408.

As shown in FIG. 4, the porous solid matrix 408 also has a cylindrical shape having an inner bore 412. In other embodiments, the porous solid matrix may have any shape known or developed in the art. The porous solid matrix 408 is positioned within the body 402 such that a space 414 is formed between the body and the porous solid matrix. At the inlet end 404 of the body 402, a diverter 410 is positioned between the inlet and the porous solid matrix 408. The diverter 410 directs the gas flow to the outer diameter of the porous solid matrix 108 (as shown by the white arrows). Gas flow is forced through the porous solid matrix 108 whereby any NO_2 is converted into NO (as shown by the darkened arrows). NO gas then exits the outlet 406 of the device 400. The porous solid matrix 408 allows the device 400 to be used in any orientation (e.g., horizontally, vertically, or at any angle). Additionally, the porous solid matrix 408 provides a rigid structure suitable to withstand vibrations and abuse associated with shipping and handling.

FIG. 5 illustrates another embodiment of a conversion cartridge 500 that generates NO from NO_2. The conversion cartridge 500 includes an inlet 505 and an outlet 510. Porous filters or a screen and glass wool 515 are located at both the inlet 505 and the outlet 510, and the remainder of the cartridge 500 is filled with a surface-active material 520 that is soaked with a saturated solution of antioxidant in water to coat the surface-active material. In the example of FIG. 5, the antioxidant is ascorbic acid.

In a general process for converting NO_2 to NO, an air flow having NO_2 is received through the inlet 505 and the air flow is fluidly communicated to the outlet 110 through the surface-active material 520 coated with the aqueous antioxidant. As long as the surface-active material remains moist and the antioxidant has not been used up in the conversion, the general process is effective at converting NO_2 to NO at ambient temperatures.

The inlet 505 may receive the air flow having NO_2, for example, from a pressurized bottle of NO_2, which also may be referred to as a tank of NO_2. The inlet 505 also may receive an air flow with NO_2 in nitrogen (N_2), air, or oxygen (O_2). The inlet 505 may also receive the air flow having NO_2 from an air pump that fluidly communicates an air flow over a permeation or a diffusion tube (not shown). The conversion occurs over a wide concentration range.

Experiments have been carried out at concentrations in air of from about 0.2 ppm NO_2 to about 100 ppm NO_2, and even to over 1000 ppm NO_2. In one example, a cartridge

that was approximately 5 inches long and had a diameter of 0.8-inches was packed with silica gel that had first been soaked in a saturated aqueous solution of ascorbic acid. Other sizes of the cartridge are also possible. The moist silica gel was prepared using ascorbic acid (i.e., vitamin C) designated as A. C. S. reagent grade 99.1 % pure from Aldrich Chemical Company and silica gel from Fischer Scientific International, Inc., designated as S8 32-1, 40 of Grade of 35 to 70 sized mesh. Other sizes of silica gel also are effective as long as the particles are small enough and the pore size is such as to provide sufficient surface area.

The silica gel was moistened with a saturated solution of ascorbic acid that had been prepared by mixing 35% by weight ascorbic acid in water, stirring, and straining the water/ascorbic acid mixture through the silica gel, followed by draining. In one embodiment, the silica gel is dried to about 30% moisture by weight. It has been found that the conversion of NO_2 to NO proceeds well when the silica gel coated with ascorbic acid is moist. The conversion of $NO_2$to NO does not proceed well in an aqueous solution of ascorbic acid alone.

The cartridge filled with the moist silica gel/ascorbic acid was able to convert 1000 ppm of NO_2 in air to NO at a flow rate of 150 ml per minute, quantitatively, non-stop for over 12 days. A wide variety of flow rates and NO_2 concentrations have been successfully tested, ranging from only a few ml per minute to flow rates of up to approximately 5,000 ml per minute, up to flow rates of approximately 80,000 ml per minute. The reaction also proceeds using other common antioxidants, such as variants of vitamin E (e.g., alpha tocopherol and gamma tocopherol).

The various embodiments described above are provided by way of illustration only and should not be construed to limit the claimed invention. Those skilled in the art will readily recognize various modifications and changes that may be made to the claimed invention without following the example embodiments and applications illustrated and described herein, and without departing from the true spirit and scope of the claimed invention, which is set forth in the following claims.

WHAT IS CLAIMED:

1. A system for delivering nitric oxide to a patient, comprising:

a patient monitor configured to monitor blood oxygen level in the patient;

a gas source to provides a gas flow having a dosage amount of nitrogen dioxide based on the monitored blood oxygen level in the patient;

one or more conversion devices operably coupled to the gas source, wherein the conversion devices convert nitrogen dioxide into nitric oxide;

and

a patient interface operably coupled to the conversion devices, wherein the patient interface delivers the dosage amount of the nitric oxide to the patient.

2. The system of claim 1, wherein the gas source includes a ventilator.

3. The system of claim 2, further comprising a humidifier positioned between the ventilator and the one or more conversion devices.

4. The system of claim 1, wherein the patient monitor includes an oxygen pulse oximeter.

5. The system of claim 4, further comprising a feedback controller that regulates the nitric oxide dose based on a reading from the oxygen pulse oximeter.

6. A method for delivering nitric oxide to a patient, comprising:

monitoring blood oxygen level in the patient;

providing a dosage amount of nitrogen dioxide based on the monitored blood oxygen level in the patient;

converting the nitrogen dioxide into nitric oxide;

and

supplying the dosage amount of the nitric oxide to the patient.

7. The method of claim 6, wherein the gas source includes a ventilator.

8. The method of claim 7, further comprising a humidifing a gas including the nitric oxide.

9. The method of claim 6, wherein the patient is monitored with an oxygen pulse oximeter.

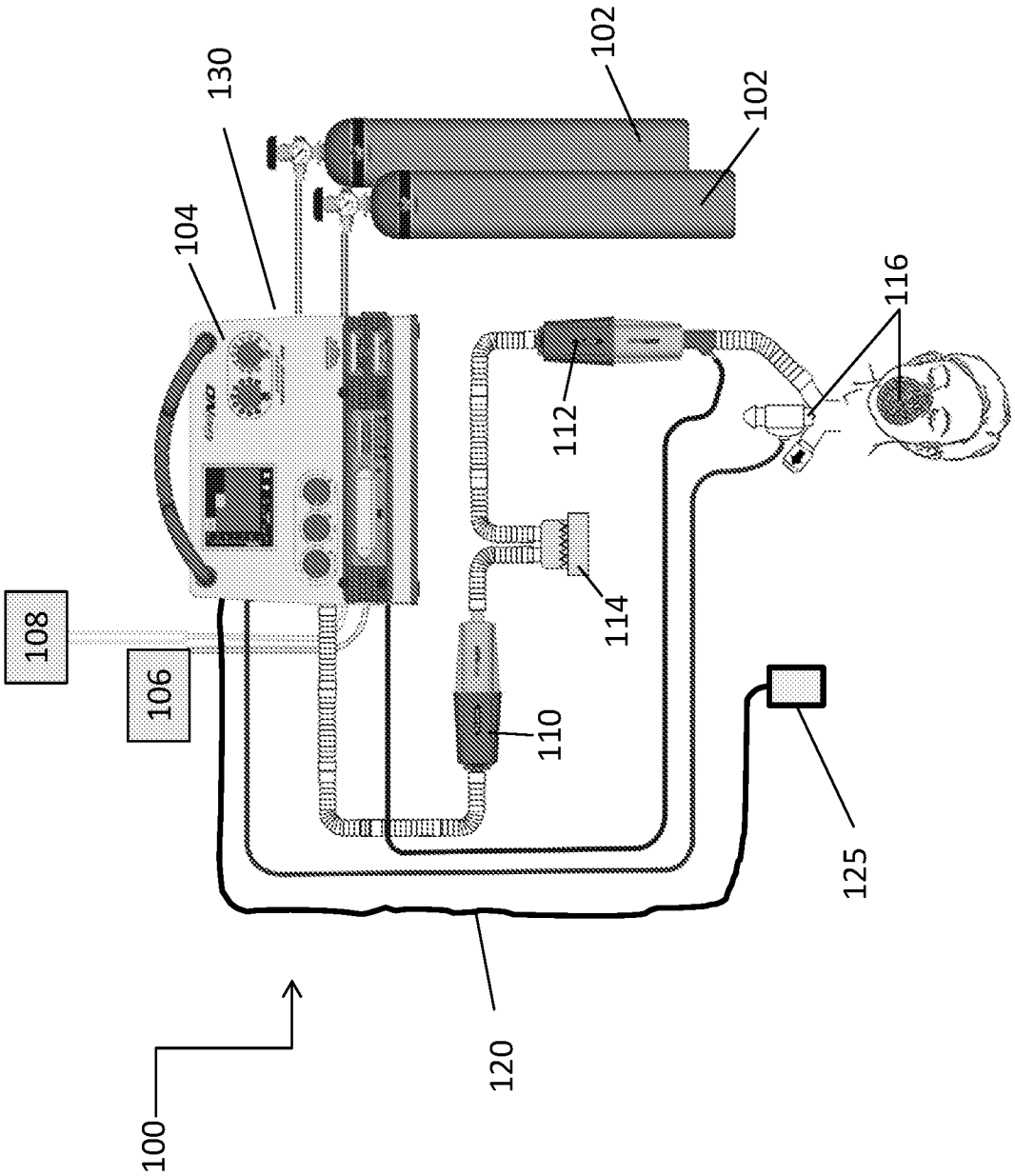


FIG. 1

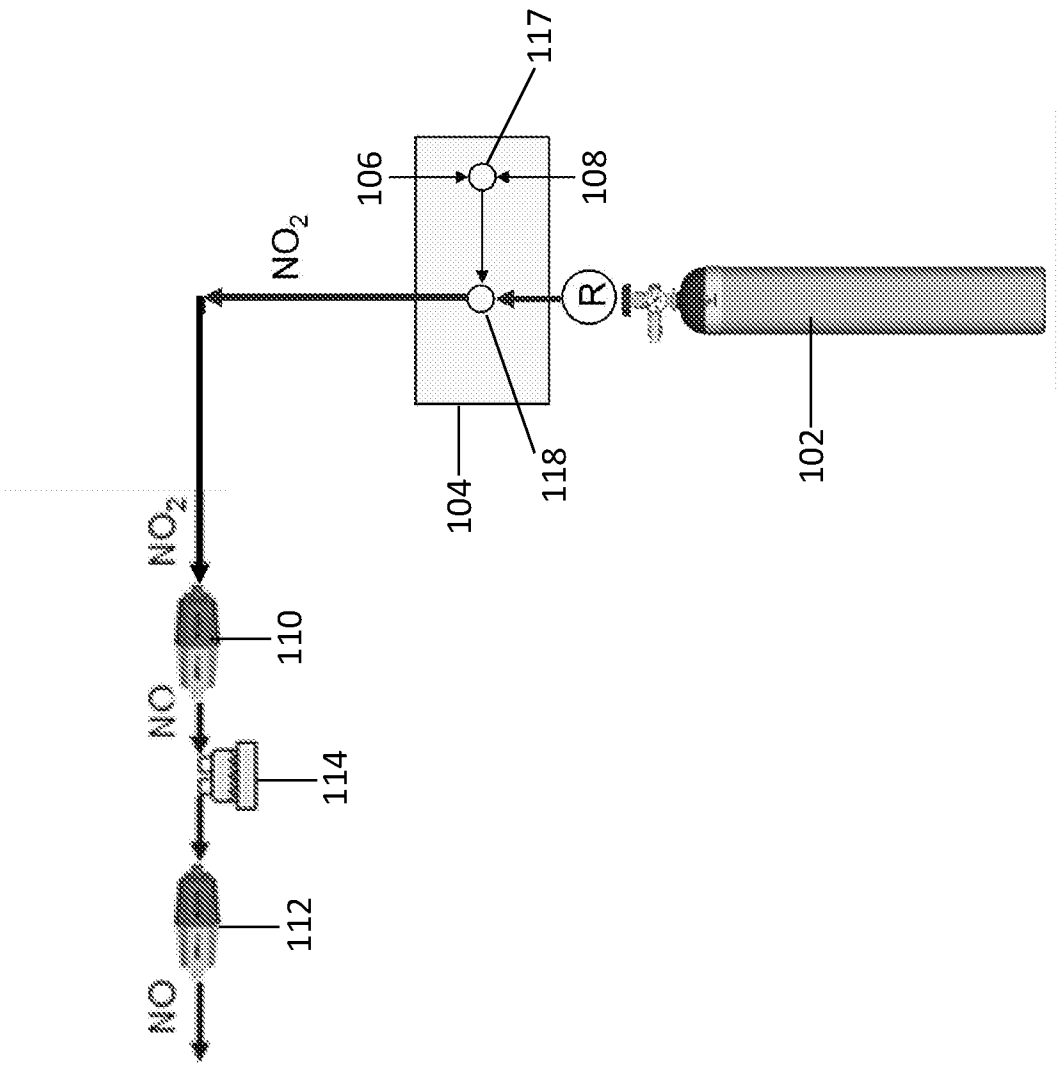


FIG. 2

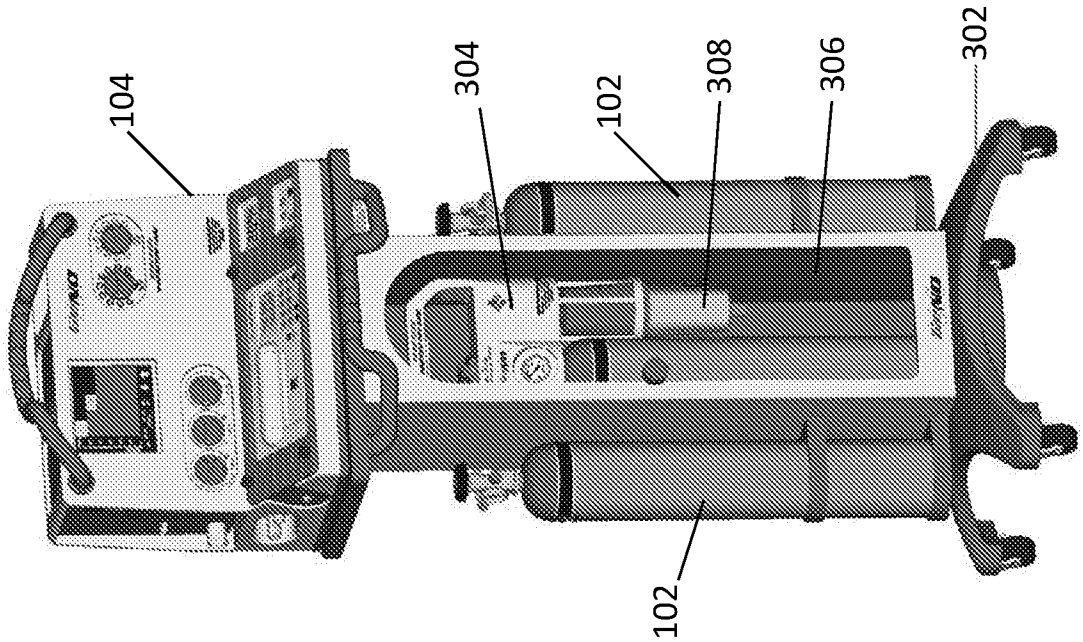


FIG. 3

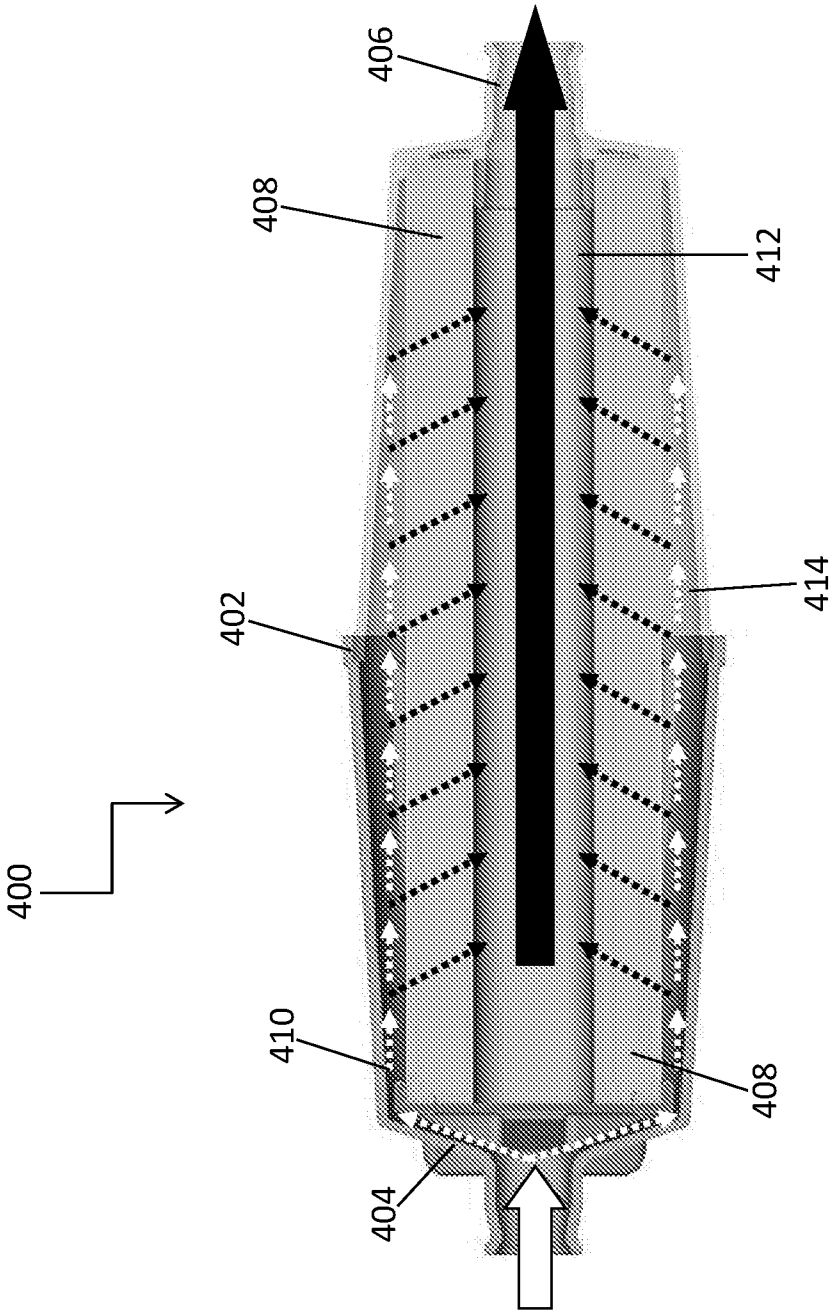


FIG. 4

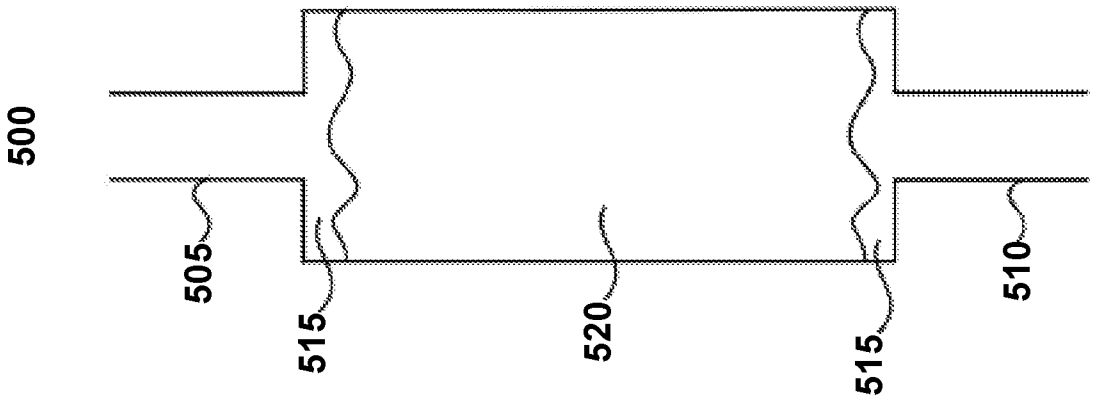


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/34198

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B5/1455; A61M16/10, 16/16 (2016.01)
CPC - A61B5/4839, 5/14551; A61M16/0003, 16/10, 16/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) Classifications: A61B5/1455; A61M16/10, 16/16 (2016.01)
CPC Classifications: A61B5/4839, 5/14551; A61M5/14542, 16/0003, 16/10, 16/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar, EBSCO, Pubmed
Nitric Oxide, Nitrogen Oxide, Nitrogen Monoxide, NO, deliver, discharge, supply, feed, dispense, blood oxygen, oxygen saturation, O2 saturation, oxygenation, oximeter, SO2, SaO2, monitor, detect, sense, measure, dose, prescribe, meter, convert, transform, generate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0240019 A1 (FINE DH et al.) October 6, 2011; paragraphs [0004], [0018], [0027], [0033]; claim 25	1-9
Y	US 7,861,717 B1 (KREBS C) January 4, 2011; column 3 lines 5-7, 59-60, column 6 lines 1-5, column 7 lines 12, 28, 32-33, 60	1-9
Y	WO 2010/021944 A1 (GENO LLC) February 25, 2010; paragraph [0018]; claim 3	3, 8
A	US 2014/0275901 A1 (INO THERAPEUTICS LLC) September 18, 2014; entire document	1-9
A	US 2015/0044305 A1 (ADVANCED INHALATION THERAPIES LTD.) February 12, 2015; entire document	1-9
A	WO 1998/047555 A1 (INSTRUMENTARIUM CORPORATION) October 29, 1998; entire document	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2016 (28.07.2016)	25 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272 4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)