

DEVICES, SYSTEMS, AND METHODS FOR ADMINISTERING HYDROGEN GAS**BACKGROUND OF THE INVENTION**

- Molecular hydrogen has been found to be of potential therapeutic use for a variety of diseases and injuries (see, e.g., Yoritaka A et al., *Neurol Sci.* 2021;42(11):4767-4770; Liu, Boyan et al., *Mol Med Rep*, vol. 22,4 (2020): 2860-2868; Ostojic SM, *Ther Adv Respir Dis.* 2020;14:1753466620951051; etc.).
- Devices for administering hydrogen gas to a subject either suffer from insufficient flow rates or concentrations of hydrogen delivered, or present unacceptable risk of creating explosive hydrogen-air gas mixtures.
- Accordingly, there is a need for new devices, systems, and methods for administering hydrogen to a subject.

SUMMARY OF THE INVENTION

- The invention provides devices, systems, and methods for providing hydrogen gas mixtures to a subject.
- An aspect of the invention provides a device for administering hydrogen to a subject. The device includes a source of hydrogen, a source of oxygen, a mixing chamber in fluid communication with the source of hydrogen and the source of oxygen; and a conduit in fluid communication with the mixing chamber. The device allows hydrogen and oxygen to be mixed to provide mixed gas at a flow rate that does not inhibit normal breathing, e.g., provides mixed gas at a rate of up to 60 liters per minute, e.g., 4-12 liters per minute (LPM).
- In some embodiments, the device provides a flow of the mixed gas to the subject at a rate of 4-8 LPM. In some embodiments, the device provides a flow of the mixed gas at a rate that matches a minute ventilation rate of the subject. In some embodiments, the device further includes a reservoir for the mixed gas. In some embodiments, the device further includes a source of a third gas (e.g., a therapeutic gas, e.g., nitrous oxide, gasotransmitters (such as carbon monoxide, hydrogen sulfide, and/or nitric oxide (e.g., each at less than 25 ppm, e.g., 1-25 ppm, e.g., 1-10 ppm, e.g., 5-10 ppm, e.g., about 8 ppm), xenon, argon, halothane, isoflurane, desflurane, sevoflurane, etc.) in fluid communication with the mixing chamber. In some embodiments, a hydrogen concentration of the mixed gas is from 0.1% to 90% (e.g., from 0.1% to 10%, e.g., from 4% to 10%, e.g., up to 80%, with the remaining 20% being oxygen).
- In some embodiments, the device further includes an interface with the subject. In some embodiments, the interface is an oral nasal mask, a nasal canula, a pair of goggles, an earpiece, a full-face mask, a helmet, a full-body suit, a chamber, an animal cage, or a sealable tube. In some embodiments, the interface includes a light source for red light therapy.
- In some embodiments, the device further includes one or more flow regulators between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof. In some embodiments, the device further includes one or more one-way valves, e.g., between the mixing

chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof. In some embodiments, the one or more one-way valves allow gas flow to the subject or from the subject, e.g., allows exhalation to the atmosphere. In some embodiments, the one or more one-way valves prevent gas flow to the subject unless opened by a negative pressure produced by an intake of breath.

- 5 In some embodiments, the device further includes a light source for red light therapy.

In some embodiments, the source of oxygen is an air pump, and the source of the third gas is a pure or concentrated oxygen source. In some embodiments, the source of hydrogen is an electrolytic hydrogen generator, a compressed gas cylinder, or a sealable cannister configured for use with a hydrogen generating composition. In some embodiments, the device further includes a computer configured to control flows of hydrogen and oxygen to the mixing chamber. In some embodiments, the device includes a humidifier in fluid communication with the mixing chamber.

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In another aspect, the invention provides a system for administering hydrogen to a subject. The system includes a device with a mixing chamber including first and second inlets and an outlet, and a conduit in fluid communication with the mixing chamber. The system further includes a source of hydrogen in fluid communication with the first inlet and a source of oxygen in fluid communication with the second inlet. The system allows hydrogen and oxygen to be mixed to provide a mixed gas at a flow rate that does not inhibit normal breathing.

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In some embodiments, the system further includes a reservoir for the mixed gas.

In some embodiments, the system further includes an interface with the subject. In some embodiments, the interface is an oral nasal mask, a nasal cannula, a full-face mask, a pair of goggles, an earpiece, a helmet, a full-body suit, a chamber, an animal cage, or a sealable tube. In some embodiments, the interface includes a light source for red light therapy.

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In some embodiments, the mixing chamber includes a third inlet and further includes a source of a third gas (e.g., a therapeutic gas, e.g., nitrous oxide, gasotransmitters (e.g., nitric oxide, carbon monoxide, and/or hydrogen sulfide), xenon, argon, halothane, isoflurane, desflurane, or sevoflurane, etc.) in fluid communication with the mixing chamber.

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In some embodiments, the system further includes one or more flow regulators, e.g., between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof. In some embodiments, the system further includes one or more one-way valves between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof. In some embodiments, the one or more one-way valves allow gas flow to the subject or from the subject, e.g., allows exhalation to the atmosphere. In some embodiments, the one or more one-way valves prevent gas flow to the subject unless opened by a negative pressure produced by an intake of breath.

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In some embodiments, the system further includes a light source for red light therapy.

In some embodiments, the source of oxygen is an air pump, and the source of the third gas is a pure or concentrated oxygen source (e.g., a compressed gas cylinder or oxygen concentrator). In some

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embodiments, the source of hydrogen is an electrolytic hydrogen generator, a compressed gas cylinder, or a sealable cannister configured for use with a hydrogen generating composition.

- In some embodiments, the system provides a flow of the mixed gas to the subject at a rate of up to 60 LPM, e.g., 4-8 LPM, 4-12 LPM, etc. In some embodiments, the system provides a flow of the mixed gas at a rate that matches a minute ventilation rate of the subject. In some embodiments, the hydrogen concentration is from 0.1% to 90% (e.g., from 0.1% to 10%, e.g., from 4% to 10%, e.g., from 4% to 90%).

In some embodiments, the system further includes a computer configured to control a flow of hydrogen and/or a flow of oxygen to the mixing chamber. In some embodiments, the system includes a humidifier in fluid communication with the mixing chamber.

- In another aspect, the device provides a method for administering hydrogen to a subject. The method includes providing a source of hydrogen, a source of oxygen, and a device with a mixing chamber and a conduit in fluid communication with the mixing chamber. The method further includes providing hydrogen from the hydrogen source and oxygen from the oxygen source to the mixing chamber to create a mixed gas, and allowing the mixed gas to flow to the subject via the conduit to provide a concentration of hydrogen at a flow rate that does not inhibit normal breathing.

- In some embodiments, the method further includes providing a third gas (e.g., a therapeutic gas, e.g., nitrous oxide, gasotransmitters (e.g., nitric oxide, carbon monoxide, and/or hydrogen sulfide), xenon, argon, halothane, isoflurane, desflurane, or sevoflurane, etc.) to the mixing chamber from a third gas source. In some embodiments, the hydrogen source and the oxygen source are integral to the device. In some embodiments, the third gas source is integral to the device.

In some embodiments, the mixed gas flows to the subject at a rate of up to 60 LPM, e.g., 4-8 LPM, 4-12 LPM, etc. In some embodiments, the mixed gas flows to the subject at a rate that matches a minute ventilation rate of the subject. In some embodiments, the mixed gas flows to the subject with a volumetric hydrogen concentration of from 0.1% to 90% (e.g., 4% to 90%).

- In some embodiments, the method further includes adjusting a flow of hydrogen from the hydrogen source and/or a flow of oxygen from the oxygen source to raise or decrease a concentration of hydrogen in the mixed gas. In some embodiments, the adjusting is via a computer that automatically adjusts a flow of hydrogen and/or oxygen to maintain a constant total flow rate.

- In some embodiments, the subject is performing physical activity and/or a breathing technique. In some embodiments, the method includes adding humidity to the mixed gas. In some embodiments, the method includes illuminating the subject with red light.

Definitions

Concentrations provided herein are % vol., i.e., volumetric concentrations.

- As used herein, the term “about” refers to $\pm 10\%$ of a recited value.

As used herein, the term “cosmetic” refers to administering a hydrogen gas mixture to all or a part of the human body, e.g., hands, face, arms, or legs, for beautifying, promoting attractiveness, or altering the appearance.

As used herein, the term “fluidically connected” refers to a direct connection between at least two device elements, e.g., a mixing chamber, a reservoir, a gas source, the interface, etc., that allows for fluid (e.g., a gas) to move between such device elements without passing through an intervening element.

As used herein, the term “in fluid communication with” refers to a connection between at least two device elements, e.g., a mixing chamber, a reservoir, a gas source, the interface, etc., that allows for fluid (e.g., gas) to move between such device elements with or without passing through one or more intervening device elements.

As used herein, the term “subject” refers to any mammal capable of being administered (e.g., topically, ocularly, by inhalation, etc.) a hydrogen gas mixture produced by a device or system of the invention. Mammals capable of being treated with devices, systems and methods of the invention include primates (e.g., humans, apes), livestock (e.g., cows, pigs, sheep), beasts of burden (e.g., ox, horse, llama), and companion animals (e.g., dogs, cats). A preferred subject is a human.

As used herein, the term “photobiomodulation therapy” refers to the use of light to treat a disease or condition (e.g., topical exposure of light) or produce a cosmetic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a scheme of a device as described herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides devices and systems for administering hydrogen gas mixtures to a subject and methods of their use. The devices and systems can provide hydrogen gas mixtures to a subject at therapeutically relevant concentrations (e.g., above 0.1%, above 0.5%, above 1%, or above 4%, hydrogen by volume, e.g., about 1.3%, about 2.3%, etc., hydrogen by volume, or, e.g., up to 80%, e.g., 2-3%, 3-5%, 4-6%, 4-8%, 5-10%, 10-50%, 20-40%, or 60-80% hydrogen by volume) at flow rates that do not impede normal breathing or even elevated breathing (e.g., during physical activity, meditation, while performing breathing techniques, etc.). Advantageously, the invention can reduce the probability of creating explosive hydrogen-air mixtures by pre-mixing the gases to safe levels before the gases exit the device or system.

Devices and Systems

Devices of the invention include a mixing chamber, e.g., a volume into which hydrogen and another gas including oxygen (e.g., air from the atmosphere (e.g., via an air pump), an oxygen cylinder, an oxygen-rich air or pure oxygen from an oxygen concentrator, etc.) are mixed. When hydrogen and the oxygen source (e.g., an air pump) are included in the device, the mixing chamber is advantageously disposed

close to the gas sources. The mixing chamber is in fluid communication with (e.g., fluidically connected to) a conduit (e.g., a piece of tubing, e.g., rubber (e.g., natural rubber, latex rubber, silicone rubber, cross-linked polyalkylene rubber, etc.) or plastic (e.g., polyethylene, polypropylene, PTFE, etc.)). The mixing chamber may be flexible or collapsible (e.g., a bag, accordion structure, or bladder) or rigid (e.g., a cylinder, a bottle, canister, etc.) container. The mixing chamber may be made of any material that can contain a gas, e.g., glass, rubber, plastic, metal, or a combination thereof. The mixing chamber may be of a volume that is greater than a volume of a subject's lungs, e.g., greater than 6 L, e.g., about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 L, e.g., about 6-20 L, e.g., about 6-10 L, 8-12 L, 10-14 L, 14-18 L, 16-20 L, 20-30 L, 20-40 L, 30-40 L, 30-60 L, 40-50 L, 40-80 L, 50-60 L, 60-70 L, 60-80 L, 70-80 L, 80-100 L, or 90-100 L. The mixing chamber may include inlets (for connection to gas sources) and outlets (for connection to the conduit). Devices may also include a separate reservoir, such as an inflatable bag e.g., between the mixing chamber and the conduit or between the conduit and the subject, to hold mixed gas produced in the mixing chamber. A reservoir may be of the same material as the mixing chamber or a difference material (e.g., a rigid reservoir and a flexible mixing chamber, or vice versa). The mixing chamber may be a reservoir. A reservoir may have a volume of, e.g., about 6-100 L, e.g., about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 L, e.g., about 6-10 L, 8-12 L, 10-14 L, 14-18 L, 16-20 L, 20-30 L, 20-40 L, 30-40 L, 30-60 L, 40-50 L, 40-80 L, 50-60 L, 60-70 L, 60-80 L, 70-80 L, 80-100 L, or 90-100 L.

Devices and systems may also include an interface for delivering the mixed gas to a subject. An interface may be any component connected to the end of the conduit (i.e., the opposite end of the conduit from the mixing chamber) that can deliver the flow of gases from the mixing chamber to the subject. The type of interface may depend on the type of treatment the subject is receiving, e.g., topical, pulmonary, or combination thereof. The interface may deliver the mixed gas to the subject so that it can be breathed in addition to or instead of ambient air. The interface may be a mask (e.g., an oral nasal mask, a full-face mask, an eye mask, a non-rebreather mask, etc.). The interface may be a helmet (e.g., a pressurizable ventilation helmet). The interface may be designed to administer hydrogen topically, e.g., to a limb, or other enclosable portion of the body (e.g., torso), e.g., via a tube or sleeve with a sealable open end (e.g., that seals around the limb or torso). The interface may be a nasal canula, a pair of goggles, or an earpiece. The interface may be a full-body suit or a walk-in/sit-in chamber (e.g., a chamber, such as a hyperbaric chamber, or an animal cage). Subject-contacting interfaces may be of any suitable material, e.g., medical grade polymers (e.g., silicone).

Devices and systems may include one or more valves (e.g., one-way/non-return valves, pressure relief valves, etc.), flow meters, flow controllers, flow restrictors, etc. One-way valves may be used to prevent dilution of the hydrogen gas mixture in the mixing chamber or reservoir(s) with exhaled breath. For example, a combination of two one-way valves may allow exhalation to the environment and not allow exhaled breath to flow to the mixing chamber. For example, there may be a one-way valve fluidically disposed between the conduit and the interface preventing airflow back along the conduit. Alternatively, a one-way/non-return valve may be between the conduit and the mixing chamber. An interface, e.g., helmet or mask, may include a one-way valve that allows air flow (e.g., exhalation) out but not in. Such a design reduces or prevents dilution of the mixed gas with exhaled carbon dioxide. One-way/non-return valves

between the gas sources may prevent hydrogen or oxygen from the mixing chamber entering the hydrogen or oxygen source. A pressure relief valve may be included in fluid communication with the mixing chamber. Relief valves may also be present to allow air intake from ambient in the event that the flow of mixed gas drops below a threshold. Pressure relief valves may also be in fluid communication with
 5 any gas source to prevent a dangerous over pressurization.

Devices and systems may include a computer, e.g., programmed to adjust the flow from the hydrogen source and/or the oxygen source, e.g., in response to a change in the breathing rate of the subject or the desired hydrogen and/or oxygen concentration to be delivered. A computer may also adjust the flow of a third gas, e.g., to add a therapeutic gas or to increase a flow of pure or concentrated oxygen to offset a
 10 reduction in oxygen concentration in the mixed gas versus atmosphere due to the addition of hydrogen. The computer may adjust flow by interfacing with valves, the hydrogen and/or oxygen source (e.g., by controlling the rate of gas generation), or a flow controller. A computer may also control the generation of gas or activation of relief valves in the event of over pressurization. The computer may also be programmed to run the device or system for a set time or for a desired cycle or to trigger alarms in the
 15 event of over pressurization or a change in the composition of the mixed gas. The computer may also cease gas production in the event of over pressurization or a change in mixed gas composition. Computers may be physically attached to a device or may interact with the device by wired or wireless connection as is known in the art. The device or system may be controlled via an app on a mobile computer, such as a phone or tablet. The device or system may also or alternatively be controlled by a
 20 computer interface associated with the device or system.

Device and systems of the invention are able to provide a flow of the mixed gas to the subject at a rate of at least 4 LPM, e.g., 4-8 LPM, e.g., 5-8 LPM, e.g., 5, 6, 7, or 8 LPM, or, e.g., up to 60 LPM, e.g., 8-20 LPM, 15-25 LPM, 20-30 LPM, 20-40 LPM, 30-40 LPM, 30-60 LPM, 40-50 LPM, 40-80 LPM, or 50-60 LPM. Devices and systems may be configured to provide a flow of the mixed gases at a rate that matches
 25 a minute ventilation rate of the subject (e.g., 12-25 breaths per minute) e.g., by manual adjustment or flow rates, by a series of valves, or by a computer according to a pre-programmed set of conditions). Devices and systems can deliver hydrogen to a subject at a concentration of 0.1-90 %, e.g., at least 0.1%, at least 0.5%, at least 1%, at least 2%, or at least 4%, e.g., 0.1-1%, 0.1-2%, 1-2.5%, 2-3%, 3-5%, 4-6%, 4-8%, 5-10%, 10-50%, 20-40%, or 60-80%. Devices of the invention may include a hydrogen source with
 30 sufficient hydrogen to provide the mixed gas to a subject for 5 minutes (min) to 24 hours, e.g., 5-10 min, 10-20 min, 5-30 min, 15-60 min, 20-60 min, 30-45 min, 30-60 min, 45-60 min, 45-90 min, 60-90 min, 45-75 min, 90-120 min, 100-120 min, 1-2 hours, 1-4 hours, 2-5 hours, 3-6 hours, 6-12 hours, 5-10 hours, 10-15 hours, 12-18 hours, 15-20 hours, or 18-24 hours. A device may include a hydrogen source of sufficient capacity for multiple treatments. In some embodiments, the devices and systems provide oxygen as 10-
 35 25% of the mixed gas, e.g., 18-22%.

Devices and systems of the invention may also include a device capable of providing red light or photobiomodulation therapy. For example, a device may include one or more red lights, e.g., LEDs, as part of a mask, pad, chamber, wall, helmet, wrap, blanket, or intranasal canula to illuminate the subject, or a part of the subject, in red light. Red lights may be in the interface to deliver mixed gas or may be a

separate component of the device or system. Red light LEDs may include wavelengths between 600 and 1100 nm, e.g., 600-650 nm, 650-700 nm, 700-750 nm, 750-800 nm, 800-850 nm, 850-900 nm, 900-950 nm, 950-1000 nm, 1000-1050 nm, and/or 1050-1100 nm, e.g., about 570, 590, 620, 633, 680, 760, 820, and/or 830 nm. The power may be between 1 and 1000 mW.

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Hydrogen Sources

Hydrogen sources may include electrolytic hydrogen generators (e.g., hydrolytic generators), compressed gas cylinders, storage tanks (e.g., hydride storage tanks), or a sealable and pressurizable container (e.g., a bottle, canister, etc., e.g., made of glass, metal, or plastic) including a hydrogen generating composition (e.g., compositions that react to form hydrogen, e.g., metal hydrides (e.g., lithium hydride, sodium borohydride, lithium aluminum hydride, sodium alanates, and ammonia borane, etc.), Mg-containing compositions, Al-containing compositions, nano-size silicon (e.g., as described by Folarin Erogbogbo, et al., Nano letters 13.2 (2013): 451-456), etc.; exemplary compositions are those described in U.S. Pat. No. 11,266,169), or combinations thereof. Compositions for producing hydrogen may be a tablet or powder containing a metal, e.g., magnesium or aluminum, that reacts with, e.g., water and/or an acid to form hydrogen. A hydrogen source may include a high surface area support, e.g., zeolites, silica microspheres, etc., onto/into which compressed hydrogen is adsorbed and/or absorbed. A hydrogen source may include enough hydrogen (e.g., in a compressed gas cylinder or from an electrolytic hydrogen generator) or hydrogen-generating composition (e.g., enough magnesium) to produce 4-10% hydrogen gas at a flow of up to 8 LPM for 5 minutes (min) to 12 hours, e.g., for 5-10 min, 10-20 min, 5-30 min, 15-60 min, 20-60 min, 30-45 min, 30-60 min, 45-60 min, 45-90 min, 60-90 min, 45-75 min, 90-120 min, or 100-120 min, e.g., at least 1 hour, e.g., 1-2 hours, 1-4 hours, 1-12 hours, etc., or, e.g., at least 2 hours, e.g., 2-5 hours, 3-6 hours, 4-7 hours, 5-10 hours, 6-9 hours, 6-12 hours, 8-10 hours, 9-12 hours, or 10-12 hours.

25 *Oxygen Sources*

An oxygen source may include an air pump or fan. Alternatively, or in addition, an oxygen source may include a source of pure oxygen or concentrated (e.g., super-atmospheric) oxygen concentration gas (e.g., a cylinder, a storage tank, an electrolytic oxygen generator, an oxygen concentrator, chemical reaction, etc.). Pumps may be a positive displacement compressor (e.g., a rotary screw, rotary vane, or reciprocating air compressors). Pumps may be diaphragm pumps. An air pump may include a bellows or piston. Oxygen may be produced by chemical reactions, e.g., hydrogen peroxide and catalase. Oxygen provided from ambient air may be filtered, e.g., by a HEPA filter.

Hydrogen and oxygen may both be generated by the same hydrolytic device, e.g., where the two gases are stored separately prior to mixing. As twice as much hydrogen is produced relative to oxygen, devices and systems may include an additional gas source, e.g., with more oxygen or an inert gas, to maintain appropriate hydrogen and/or oxygen levels in a non-explosive ratio.

Other Gases

A third gas may also be added to the hydrogen gas mixture by connecting a third gas source to the mixing chamber. The third gas may be a therapeutic gas (e.g., desflurane, isoflurane, halothane, nitrous oxide, sevoflurane, argon, xenon, etc.). Inert gases such as nitrogen and helium are also considered.

- 5 Therapeutic gases may also include gases such as hydrogen sulfide, carbon monoxide, ozone, and nitric oxide, at suitably low concentrations. The third gas may be or include oxygen, e.g., a pure or concentrated oxygen source, so that the concentration of oxygen received by the subject may be maintained at or above atmospheric oxygen concentration (e.g., to counteract the dilution effect of added hydrogen when an air pump is the oxygen source).

10 *Systems, Kits, and Additional Components*

- Systems of the invention may include separate gas sources, e.g., where the device does not include integrated gas sources. Gas sources may be any described herein (e.g., hydrogen generators, oxygen generators or concentrators, compressed gas cylinders, storage tanks, etc.) Systems and kits may include additional conduits (e.g., tubing and tubing connectors), e.g., for attaching a device of the invention to an external gas source. Systems may include an interface (e.g., provide together with a device in a kit). Interfaces included in systems of the invention may be any described herein (e.g., an oral nasal mask, a nasal cannula, a full face mask, a pair of goggles, an earpiece, a helmet, a full-body suit, a hyperbaric chamber, or a sealable tube or sleeve). A fixed structure (e.g., a chamber) may be part of a system of the invention. A system may also include a light source for red light therapy or photobiomodulation therapy as a separate component.
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- A system of the invention may include a device in which one or more of the hydrogen source, the oxygen source, or the third gas source is integral to the device. For example, a system may include a device with a built-in hydrogen or anesthetic gas source, while oxygen is provided by an external oxygen concentrator or cylinder. Alternatively, a system may include a device with a built-in oxygen source, e.g., a compressor or an oxygen concentrator or cylinder, and an external hydrogen source (e.g., a compressed gas cylinder) or third gas source (e.g., a nebulizer or vaporizer).
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- Systems of the invention may include components to pressurize the gas sources, e.g., pumps, pistons, actuators (e.g., mechanical, hydraulic, or pneumatic, etc., actuators), presses (e.g., mechanical, hydraulic, or pneumatic, etc., presses), piezoelectric actuators, levers, etc. A system of the invention may also include a power source, e.g., to power pumps, control valves, computers, etc. Systems of the invention may include additional pumps, reservoirs (e.g., tanks, cylinders, etc.), pressure sensors, actuators, valves, etc. Systems of the invention may include a computer (e.g., a microcontroller), e.g., for monitoring or controlling the device, e.g., to send a signal to a control valve to adjust the flow of from the hydrogen source, the oxygen source, or third gas source, and/or to open a pressure release valve to depressurize the device. In some embodiments, the system further includes additional reservoirs for mixing gases. Systems of the invention may include a nebulizer or a vaporizer (e.g., an anesthetic vaporizer). Systems of the invention may also include a humidifier (e.g., an ultrasonic humidifier, an impeller humidifier, an evaporator, or a steam vaporizer) in fluid communication with the device or system. A humidifier may be fluidically connected to the hydrogen source and/or the mixing chamber.
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Humidification of the hydrogen gas mixture can reduce the explosion risk of high (e.g., >4%) hydrogen gas mixtures, e.g., by reducing the risk of static discharge.

Methods

- Methods of the invention allow the provision of mixtures of hydrogen gas to a subject. Advantageously,
- 5 methods of the invention can provide therapeutic, e.g., >0.1%, concentrations (e.g., high concentrations, e.g., >4%) of hydrogen to a subject without inhibiting normal breathing or even elevated breathing (e.g., during exercise, certain breathing techniques, etc.). Methods of the invention can also reduce the risk of explosion when administering hydrogen to a subject by controlling the amount of hydrogen and/or ratio of hydrogen to oxygen.
- 10 Methods involve creating mixed gas by mixing hydrogen and oxygen in a device including a mixing chamber. A conduit in fluid communication with the mixing chamber then allows the mixed gases to be delivered to the subject, e.g., topically and/or pulmonary. In some embodiments, a third gas (e.g., any gas described herein) is provided to the mixing chamber from a third gas source in fluid communication with the mixing chamber.
- 15 Mixed gases can flow to the subject at rates of at least 4 LPM, e.g., about 4-8 LPM, e.g., about 5, 6, 7, or 8 LPM. The flow of the mixed gases may match a minute ventilation rate of the subject. Methods of the invention can deliver hydrogen to a subject at a concentration of 0.1-90 %, e.g., 1-10%, e.g., 0.5-4% or at least 4%, e.g., 4-6%, 4-8%, or 5-10%. The hydrogen concentration may be less than 10%. The method may deliver at least 300 mL per minute (e.g., about 300-750 mL) of hydrogen, e.g., mixed with about 7.2
- 20 LPM of other gas. The mixed gas may also provide oxygen at or near normal breathing range, e.g., about 10-25%, e.g., about 18-22%. The system may provide low oxygen concentrations (e.g., 10-20%) intermittently, e.g., for hypoxia conditioning applications.

- Methods of the invention may include providing humidity with the mixed gases, e.g., from a humidifier in fluid communication with the system (e.g., in fluid communication with the device, e.g., fluidically
- 25 connected to the hydrogen source or chamber, or, e.g., fluidically connected to the conduit). Humidity may be provided at a level that provides comfort to the subject, e.g., >10 mg/L, e.g., about 17-42 mg/L, e.g., about 17 mg/L, about 23 mg/L, about 32 mg/L, about 42 mg/L, or, e.g., about >32 mg/L, e.g., at a relative humidity of about 30-100%, e.g., 30-50 %, for the temperature and pressure of the mixed gases. Methods of the invention may include adjusting (e.g., manually or via computer) the relative
- 30 humidity of the mixed gases. A humidity level may be selected to prevent static discharge inside the system.

Methods may also include adjusting (e.g., manually or via computer) a flow of hydrogen from the hydrogen source and/or a flow of oxygen from the oxygen source and/or third gas to raise or decrease the concentration of hydrogen, oxygen, and/or third gas provided to the subject.

- 35 Methods of the invention may include providing a hydrogen gas mixture to a subject while the subject is performing physical activity (e.g., running, rowing, cycling, etc., e.g., on stationary gym equipment). Alternatively, or in addition, the subject may perform a breathing technique (e.g., breathing techniques for relaxation, pulmonary rehabilitation, meditative breathing techniques, etc.). Examples of breathing

- techniques that may be performed in combination with or as part as methods of the invention include, e.g., pursed lips breathing, belly breathing (aka diaphragmatic breathing), “4-8-8” breathing, Wim Hof breathing, 60 second inhalation and 60 second exhalation, etc. Methods may include setting a pre-programmed set of conditions for the flow of mixed gases (e.g., flow rate, pressure, oxygen concentration,
- 5 hydrogen concentration, type and concentration of additional gas, etc.) which are suited to the type of exercise or breathing technique being performed.

Example

- An exemplary device is shown in Fig 1. A water reservoir delivers water to an electrolytic cell containing a proton exchange membrane. The electrolytic cell separates water into hydrogen and oxygen gas, which
- 10 are separately collected and sent to an air blower and mixer. The air blower and mixer combine the oxygen and hydrogen gas produced from the electrolytic cell with filtered air from the room outside of the machine. The combined gas is submitted to an inflatable bag that doses the gas to a mask and the patient through a one-way valve that prevents exhaled gas from the patient from mixing with the
- 15 combined gas at the balloon. The machine can be controlled through a touch screen display that is also connected to a speaker capable of producing audible feedback. The touch screen is also connected to sensors that measure and display effluent gas percentages, air flow rate, HEPA interlock check, water level of the reservoir, machine tipping, electrolytic cell temperature, and total dissolved solids. These sensors, screen, speaker, and electrolytic cell are powered by a main power supply.
- 20 Table 1 shows the machine settings, i.e., flow settings, electrolysis current, touch screen settings, selected to produce combined gas mixtures at the mask. The measured quantities of H₂ and O₂ gas in the effluent are shown in the table.

Other embodiments are in the claims.

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Table 1

H ₂ , O ₂ , and Room-Air Blower Flow-Rate Table (SATP)														
(0.5% to 4% H ₂ , delivered flow to mask ≈ 8564 to 9043 mL/min)														
Enter Fan Flow Rate (mL/min)				8500		Fan Flow Rate (mL/sec)		142						
H ₂ % Front-Panel Selection	H ₂ + O ₂ Required %	Room-Air Blower Flow Rate	O ₂ Portion of Room Air Flow	Room-Air Minus O ₂ Flow Rate	H ₂ + O ₂ Flow Rate from PEM	H ₂ Flow Rate from PEM	O ₂ Flow Rate from PEM	Room Air + PEM H ₂ + O ₂ Flow Rate	Total O ₂ Flow Rate (PEM + Room Air)	H ₂ % of Total Flow	O ₂ % of Total Flow (O ₂ internally vented)	O ₂ % of Total Flow (O ₂ externally vented)	Electrolysis Amps (single cell)	
		mL/min	mL/min	mL/min	mL/min	mL/min	mL/min	mL/min	mL/min	mL/min				
		mL/s	mL/s	mL/s	mL/s	mL/s	mL/s	mL/s	mL/s	mL/s	mL/s			
0.50	0.8	8500.0	1780.8	6719.3	64.2	42.8	21.4	8564.2	1802.2	0.50	21.04	20.79	5.6	
		141.7	29.7	112.0	1.1	0.7	0.4	142.7	30.0					
1.00	1.5	8500.0	1780.8	6719.3	129.4	86.3	43.1	8629.4	1823.9	1.00	21.14	20.64	11.3	
		141.7	29.7	112.0	2.2	1.4	0.7	143.8	30.4					
1.50	2.3	8500.0	1780.8	6719.3	195.7	130.4	65.2	8695.7	1846.0	1.5	21.23	20.48	17.1	
		141.7	29.7	112.0	3.3	2.2	1.1	144.9	30.8					
2.00	3.0	8500.0	1780.8	6719.3	262.9	175.2	87.6	8762.9	1868.4	2.00	21.32	20.32	23.0	
		141.7	29.7	112.0	4.4	2.9	1.5	146.0	31.1					
2.50	3.8	8500.0	1780.8	6719.3	331.2	220.8	110.4	8831.2	1891.1	2.50	21.41	20.16	29.0	
		141.7	29.7	112.0	5.5	3.7	1.8	147.2	31.5					
3.00	4.5	8500.0	1780.8	6719.3	400.5	267.0	133.5	8900.5	1914.2	3.00	21.51	20.01	35.1	
		141.7	29.7	112.0	6.7	4.4	2.2	148.3	31.9					

3.50	5.3	8500.0	1780.8	6719.3	471.0	314.0	157.0	8971.0	1937.7	3.50	21.60	19.85	41.3
		141.7	29.7	112.0	7.8	5.2	2.6	149.5	32.3				
4.00	6.0	8500.0	1780.8	6719.3	542.6	361.7	180.8	9042.6	1961.6	4.00	21.69	19.69	47.5
		141.7	29.7	112.0	9.0	6.0	3.0	150.7	32.7				

What is claimed is:

CLAIMS

1. A device for administering hydrogen to a subject, the device comprising:

- a) a source of hydrogen;
- b) a source of oxygen;
- c) a mixing chamber in fluid communication with the source of hydrogen and the source of oxygen; and
- d) a conduit in fluid communication with the mixing chamber;

wherein the device allows hydrogen and oxygen to be mixed to provide a mixed gas a flow rate that does not inhibit normal breathing.

2. The device of claim 1, wherein the device provides a flow of the mixed gas to the subject at a rate of 4-60 LPM.

3. The device of claim 1, wherein the device provides a flow of the mixed gas at a rate that matches a minute ventilation rate of the subject.

4. The device of claim 1, further comprising a reservoir for the mixed gas.

5. The device of claim 1, further comprising a source of a third gas in fluid communication with the mixing chamber.

6. The device of claim 1, further comprising an interface with the subject.

7. The device of claim 6, wherein the interface is an oral nasal mask, a nasal canula, a full-face mask, a pair of goggles, an earpiece, a helmet, a full-body suit, a chamber, an animal cage, or a sealable tube.

8. The device of claim 1, further comprising one or more flow regulators between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof.

9. The device of claim 1, further comprising one or more one-way valves between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof.
10. The device of claim 9, wherein the one or more one-way valves allow gas flow to the subject.
11. The device of claim 9, wherein the one or more one-way valves prevent gas flow to the subject unless opened by a negative pressure produce by an intake of breath.
12. The device of claim 5, wherein the third gas is a therapeutic gas.
13. The device of claim 12, wherein the third gas is nitrous oxide, nitric oxide, xenon, argon, halothane, isoflurane, desflurane, carbon monoxide, hydrogen sulfide, or sevoflurane.
14. The device of claim 5, wherein the source of oxygen is an air pump, and the source of the third gas is a pure or concentrated oxygen source.
15. The device of claim 1, wherein the source of hydrogen is an electrolytic hydrogen generator, a compressed gas cylinder, or a sealable cannister configured for use with a hydrogen generating composition.
16. The device of claim 1, further comprising a computer configured to control flows of hydrogen and/or oxygen to the mixing chamber.
17. The device of claim 1, further comprising a humidifier in fluid communication with the mixing chamber.
18. The device of claim 1, further comprising a light source for red light therapy.
19. The device of claim 6, wherein the interface comprises a light source for red light therapy.
20. A system for administering hydrogen to a subject comprising:
- a) device comprising:

i) a mixing chamber comprising first and second inlets and an outlet; and

ii) a conduit in fluid communication with the mixing chamber;

b) a source of hydrogen in fluid communication with the first inlet; and

c) a source of oxygen in fluid communication with the second inlet;

wherein the system allows hydrogen and oxygen to be mixed to provide a mixed gas at a flow rate that does not inhibit normal breathing.

21. The system of claim 20, further comprising a reservoir for the mixed gas.

22. The system of claim 20, further comprising an interface with the subject.

23. The system of claim 22, wherein the interface is an oral nasal mask, a nasal canula, a full face mask, a pair of goggles, an earpiece, a helmet, a full-body suit, a chamber, an animal cage, or a sealable tube.

24. The system of claim 20, further comprising a third inlet in the mixing chamber and a source of a third gas in fluid communication with the mixing chamber.

25. The system of claim 24, wherein the third gas is nitrous oxide, nitric oxide, xenon, argon, halothane, isoflurane, desflurane, carbon monoxide, hydrogen sulfide, or sevoflurane.

26. The system of claim 24, wherein the third gas is a therapeutic gas.

27. The system of claim 20, further comprising one or more flow regulators between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof.

28. The system of claim 20, further comprising one or more one-way valves between the mixing chamber and the subject, the source of hydrogen, the source of oxygen, or a combination thereof.

29. The system of claim 28, wherein the one or more one-way valves allow gas flow to the subject.

30. The system of claim 28, wherein the one or more one-way valves prevent gas flow to the subject unless opened by a negative pressure produce by an intake of breath.

31. The system of claim 24, wherein the source of oxygen is an air pump, and the source of the third gas is a pure or concentrated oxygen source.

32. The system of claim 20, wherein the source of hydrogen is an electrolytic hydrogen generator, a compressed gas cylinder, or a sealable cannister configured for use with a hydrogen generating composition.

33. The system of claim 20, wherein the system provides a flow of the mixed gas to the subject at a rate of 4-60 LPM.

34. The system of claim 20, wherein the system provides a flow of the mixed gases at a rate that matches a minute ventilation rate of the subject.

35. The system of claim 20, further comprising a computer configured to control the flow of hydrogen and/or oxygen to the mixing chamber.

36. The system of claim 20, further comprising a humidifier in fluid communication with the mixing chamber.

37. The system of claim 20, further comprising a light source for red light therapy.

38. The system of claim 22, wherein the interface comprises a light source for red light therapy.

39. A method for administering hydrogen to a subject comprising:

a) providing a device comprising:

i) a mixing chamber

ii) a conduit in fluid communication with the mixing chamber; and

b) providing hydrogen from a hydrogen source and oxygen from an oxygen source to the mixing chamber to create a mixed gas; and

c) allowing the mixed gas to flow to the subject via the conduit to provide the mixed gas at a flow rate that does not inhibit normal breathing.

40. The method of claim 39, further comprising providing a third gas to the mixing chamber from a third gas source.

41. The method of claim 40, wherein the third gas is nitrous oxide, nitric oxide, xenon, argon, halothane, isoflurane, desflurane, carbon monoxide, hydrogen sulfide, or sevoflurane.

42. The method of claim 39, wherein the mixed gas flows to the subject at a rate of 1-60 LPM.

43. The method of claim 39, wherein the mixed gas flows to the subject at a rate that matches a minute ventilation rate of the subject.

44. The method of claim 39, further comprising adjusting a flow of hydrogen from the hydrogen source and/or a flow of oxygen from the oxygen source to raise or decrease a concentration of hydrogen provided to the subject in the mixed gas.

45. The method of claim 44, wherein the adjusting occurs via a computer that automatically adjusts the flow of hydrogen and/or oxygen to maintain a constant total flow rate.

46. The method of claim 39, wherein the subject is performing physical activity and/or a breathing technique.

47. The method of claim 39, further comprising adding humidity to the mixed gas.

48. The method of claim 1, further comprising illuminating the subject with red light.