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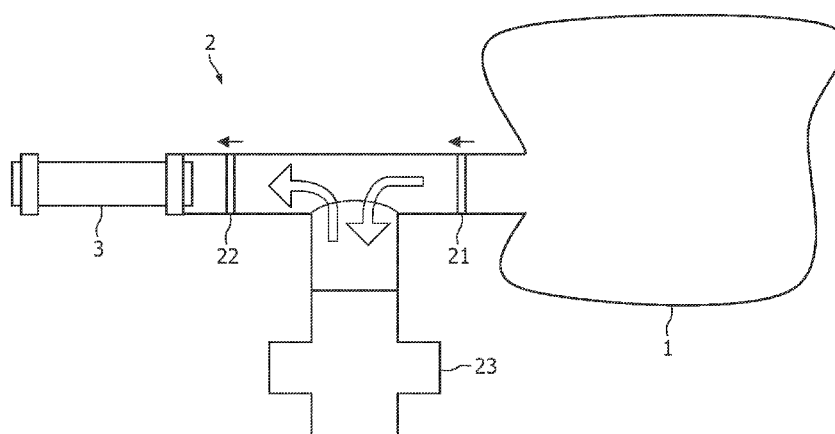


FIG. 1

(57) Abstract: The present invention relates to a simple, efficient and accurate breath collection device and a corresponding method for collecting the breath of a patient for analysis. The device comprises a gas mixture container (1) containing a gas mixture for inhalation by the patient, and a breathing unit (2) containing an inlet (21) connected to said gas mixture container (1) for letting in gas from the gas mixture container (1), an outlet (22) for letting out gas exhaled by the patient and a breathing element (23) for inhaling gas from the inlet (21) and exhaling gas to the outlet (22). The gas mixture container (1) contains a gas mixture containing a predetermined set of volatile organic compounds (VOC) markers.



BREATH COLLECTION DEVICE AND METHOD

FIELD OF THE INVENTION

The present invention relates to a breath collection device and a corresponding method for collecting the breath of a patient for analysis.

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BACKGROUND OF THE INVENTION

US 2003/065274 A discloses a method of determining a respiratory parameter for a subject using an indirect calorimeter. The indirect calorimeter includes a respiratory connector for passing inhaled and exhaled gases, a flow pathway operable to receive and pass inhaled and exhaled gases having a flow tube within the flow pathway through which the inhaled and exhaled gases pass, a flow meter for determining an instantaneous flow volume of the inhaled and exhaled gases, a component gas concentration sensor for determining an instantaneous fraction of a predetermined component gas and a computation unit having a processor and a memory. Generally, the subject inhales atmospheric gas, but it is also disclosed that instead other gas mixtures from a source of respiratory gases can be inhaled. Further, it is disclosed that the exhaled air can be provided to other analytical devices for further analysis, e.g. to find indicators of lung disease or cancer.

20 SUMMARY OF THE INVENTION

It is an object of the present invention to provide a simple, efficient and accurate breath collection device and a corresponding method for collecting the breath of a patient for analysis.

In a first aspect of the present invention a breath collection device for collecting the breath of a patient for analysis is presented comprising a gas mixture container containing a gas mixture for inhalation by the patient, and a breathing unit containing an inlet connected to said gas mixture container for letting in gas from the gas mixture container, an outlet for letting out gas exhaled by the patient and a breathing element for inhaling gas from the inlet and exhaling gas to the outlet, which is characterized in that said gas mixture container contains a gas mixture containing a predetermined set of volatile organic compounds (VOC) markers.

In a further aspect of the present invention a breath collection method for collecting the breath of a patient for analysis is presented, comprising the steps of:

- providing a gas mixture for inhalation by the patient,
- allowing the patient to inhale the provided gas mixture via an inlet,
- 5 - passing the gas exhaled by the patient to an outlet,

which is characterized in that said provided gas mixture contains a predetermined set of volatile organic compounds (VOC) markers.

Preferred embodiments of the invention are defined in the dependent claims. It shall be understood that the claim method has similar and/or identical preferred embodiments as the claimed device and as defined in the dependent claims.

Normal human breath contains a large number of volatile organic compounds (VOCs). It is known that a sample of breath contains hundreds of different VOCs, mostly in nano- and picomolar concentrations (i.e. 10^{-9} - 10^{-12} mol/L). Recent clinical studies show that the altered abundance of these VOCs in breath can be used to predict disease state. There are, however, a number of serious problems when sampling VOCs in breath as biomarkers for disease.

The environmental atmosphere contains a wealth of VOCs, which can be inhaled and exhaled again. Therefore, it is most likely that the spectrum of exhaled VOCs is substantially influenced by the components in the local environment. There are several ways to deal with this background problem:

- i) ignore it; or
- ii) filter the inhaled air; or
- iii) use a differential measurement: $[\text{VOC}]_n (\text{breath}) - [\text{VOC}]_n (\text{air})$.

Obviously, the first suggestion is straightforward but wrong. The second suggestion is difficult to carry out in practice, since filters often appear to be the origin of contaminations (it should be recalled that concentration levels are in the ppt-ppb regime). Therefore, only the latter option is available, which appears to be the most accurate procedure. However, in that case the results will depend on the exact composition of the inhaled air. The latter can vary substantially depending on the location of the measurement: for instance, city versus rural area, hospital area versus regular office area, proximity to highways and airports, proximity to industry plants etc..

A second problem is related to the occurrence of so-called negative biomarkers, which can be reasoned as follows. The lung system inhales components from the environment and subsequently these can be absorbed and/or metabolised by the body.

Consequently, the concentration of that particular component is higher in the inhaled air than in the exhaled air. In case these components are considered typical for a disease state this can be called negative biomarkers (the differential measurement as discussed earlier will yield negative values).

5 Obviously, for both the background problem as well as the issue of the negative biomarkers the inhaled air composition needs to be controlled which is the basic idea of the present invention.

In particular, a breath collection device is proposed by the present invention where the inlet is connected to a container, e.g. a gas cylinder, gas sampling bag etc.. The gas
10 container is preferably filled with normal humidified air plus a specific set of VOC markers. Generally, the concentration of these VOCs will be very low (ppt-ppb level), and therefore the inhaled air mixture poses absolutely no harm to the patient. In this way the above problems can be overcome and the influence of the patient on the predetermined VOC profile contained in the exhaled gas can be exactly determined. An analysis of negative
15 biomarkers can thus be made with high accuracy.

Thus, the present invention makes use of the concept that the absorption and metabolization of inhaled, artificial (i.e. not endogenous or origin) VOCs depends on disease state. The invention is different from and not just a simple extension of measuring metabolism using oxygen consumption or carbon dioxide generation.

20 To further improve the accuracy of the method and to separate the added VOCs from the natural occurring VOCs, labelled compounds with deuterium (^2H) and/or stable carbon isotope (^{13}C) can be used as proposed according to a further embodiment.

The exact composition of the VOC mixture will depend on the type of disease being screened using the breath collection device. Preferred VOC markers are from the group
25 comprising alkanes, aromatics, alcohols, aldehydes, ketones and/or their labelled equivalents. It is to be understood that these markers are examples, the above list is not a complete list)

According to a further embodiment said inlet and said outlet of said breathing unit comprise one-way valves to ensure that the patient is only inhaling the gas mixture from the gas mixture container and is only exhaling via the outlet and not via the inlet.

30 In a further embodiment an analysis unit connected to said outlet of said breathing unit for analysis of the exhaled gas is provided. Thus, already during the breathing an analysis of the exhaled gas can be made online.

Preferably, said analysis unit is adapted for performing a differential analysis of the VOC marker profile contained in the gas mixture container versus the VOC marker profile contained in the exhaled gas.

In an alternative embodiment a VOC sampling unit for sampling the VOC marker profile contained in the exhaled gas is provided. This enables an offline analysis of the exhaled gas.

To make sure that the actual measurement is not falsified by VOCs still being in the lung, in an initial step the patient can be made to inhale a gas mixture containing no VOC markers first, before he inhales the gas mixture containing the predetermined set of VOC markers. An appropriate embodiment thus comprises:

- an air container each containing an air mixture containing no VOC markers and
- a switching unit having a switching outlet connected to the inlet of said breathing unit and one or more switching inlets connected to said air container and said gas mixture container, respectively, for switching there between so that either the air mixture contained in the air container or the gas mixture contained in the gas mixture container can be inhaled from the patient.

Even further, in an embodiment one or more additional gas mixture containers containing a predetermined air mixture containing predetermined set of VOC markers and a switching unit allowing to switch between the different gas mixture containers for inhalation by the patient are provided so that, for instance, a desired step-wise inhalation procedure can be performed, wherein in each step a different gas mixture is provided for inhalation.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other aspects of the invention will be apparent from and elucidated with reference to the embodiment(s) described hereinafter. In the following drawings

Fig. 1 schematically shows a first embodiment of a breath collection device according to the present invention,

Fig. 2 schematically shows a second embodiment of a breath collection device according to the present invention, and

Fig. 3 schematically shows a third embodiment of a breath collection device according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 shows a first embodiment of a breath collection device according to the present invention for collecting the breath of a patient for analysis, e.g. for analysis of biomarker indicating a disease. The device comprises a gas mixture container 1 containing a gas mixture for inhalation by the patient, said gas mixture containing a set of VOC biomarkers. The device further comprises a breathing unit 2 containing an inlet 21 connected to said gas mixture container 1 for letting in gas from the gas mixture container 1, an outlet 22 for letting out gas exhaled by the patient and a breathing element 23 for inhaling gas from the inlet 21 and exhaling gas to the outlet 22. One-way valves are mounted in the inlet 21 and the outlet 22 to circumvent re-breathing by the patient. The outlet 22 is connected to a VOC sampler 3 wherein the exhaled VOCs are being collected. The arrows depict the air stream when a person is breathing through the breathing element 23, e.g. a mouthpiece or a mask covering mouth and nose.

An accurate differential analysis of the VOC profile can be obtained by analysing the VOCs in the gas mixture container 1 and in the VOC sampler 3. This analysis can be performed offline, e.g. using standard gas analysis techniques such as gas chromatography and mass spectrometry.

Fig. 2 shows a second embodiment of a breath collection device according to the present invention. In order to reduce the background effect prior to the actual measurement, the patient can be breathing with the device with an air container 4, e.g. with standardized air without the presence of any biomarker VOCs. After a proper time, sufficient for removal of interfering trace-gases in the air content of the lungs from inhalation prior to the experiment, the device can switch by a switch 5 to the gas mixture container 1 which has the controlled presence of the biomarker VOCs in the standardized air. For this purpose the switch comprises a switching outlet 51 connected to the inlet 21 of said breathing unit 2 and one or more switching inlets 52, 53 connected to said air container 4 and said gas mixture container 1, respectively, for switching there between. Thus, either the air mixture contained in the air container 4 or the gas mixture contained in the gas mixture container 1 can be inhaled from the patient.

Fig. 3 shows a second embodiment of a breath collection device according to the present invention. This embodiment comprises a number n of gas mixture containers 11, 12, .., 1n each containing a different gas mixture containing a different predetermined set of VOC markers. This allows to perform a procedures with a number of steps where

consecutively the different gas mixtures provided to the patient for inhalation via the switch 5, in case the disease needs to be characterized by such a sequence of operations.

Of course, the air container 4 shown in Fig. 2 may also be provided in addition for initial use or for use in between the different steps for "neutralizing" the lung content of the patient.

Instead of the VOC sampler 3 an analysis unit 6 is provided for direct analysis of the exhaled gas (preferably online).

Obviously, the shown embodiments are relatively simple embodiments of the breath collection device. Depending on the breath experiment and the sampling requirements (e.g. single exhalation, tidal breathing, sampling of higher, middle or lower respiratory tract, etc.) the device can be more advanced. The basic idea, however, is the use of at least one container/sampling bag at the inlet, which contains a specific set of VOC biomarkers with known concentrations. Possible VOCs are alkanes (pentane, hexane, heptane, cyclohexane), aromatics (toluene, xylene), alcohols (ethanol, propanol, butanol), aldehydes, ketones (butanal, acetone, butanon) and their labelled equivalents.

While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments. Other variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims.

In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. A single element or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measured cannot be used to advantage.

Any reference signs in the claims should not be construed as limiting the scope.

CLAIMS:

1. Breath collection device for collecting the breath of a patient for analysis, comprising:
 - a gas mixture container (1) containing a gas mixture for inhalation by the patient, and
 - 5 - a breathing unit (2) containing an inlet (21) connected to said gas mixture container (1) for letting in gas from the gas mixture container (1), an outlet (22) for letting out gas exhaled by the patient and a breathing element (23) for inhaling gas from the inlet (21) and exhaling gas to the outlet (22), characterized in that said gas mixture container (1) contains a gas mixture containing a
10 predetermined set of volatile organic compounds (VOC) markers.
2. Breath collection device as claimed in claim 1, wherein said gas mixture container (1) contains VOC markers which have been labelled with a labelling component, in particular with deuterium and/or carbon.
15
3. Breath collection device as claimed in claim 1, wherein said gas mixture container (1) contains VOC markers from the group comprising alkanes, aromatics, alcohols, aldehydes, ketones and/or their labelled equivalents.
- 20 4. Breath collection device as claimed in claim 1, wherein said inlet and said outlet (22) of said breathing unit (2) comprise one-way valves.
5. Breath collection device as claimed in claim 1, further comprising an analysis unit (6) connected to said outlet (22) of said breathing unit (2)
25 for analysis of the exhaled gas.
6. Breath collection device as claimed in claim 1,

wherein said analysis unit (6) is adapted for performing a differential analysis of the VOC marker profile contained in the gas mixture container (1) versus the VOC marker profile contained in the exhaled gas.

- 5 7. Breath collection device as claimed in claim 1,
further comprising a VOC sampling unit (3) for sampling the VOC marker profile contained
in the exhaled gas.
8. Breath collection device as claimed in claim 1,
10 further comprising:
- an air container (4) each containing an air mixture containing no VOC markers
and
- a switching unit (5) having a switching outlet (51) connected to the inlet (21)
of said breathing unit (2) and one or more switching inlets (52, 53) connected to said air
15 container (4) and said gas mixture container (1), respectively, for switching there between so
that either the air mixture contained in the air container (4) or the gas mixture contained in
the gas mixture container (1) can be inhaled from the patient.
9. Breath collection device as claimed in claim 1,
20 further comprising:
- one or more additional gas mixture containers (11, 12, ..., 1n) containing a
predetermined air mixture containing predetermined set of VOC markers and
- a switching unit (5) allowing to switch between the different gas mixture
containers (11, 12, ..., 1n) for inhalation by the patient.
- 25 10. Breath collection method for collecting the breath of a patient for analysis,
comprising the steps of:
- providing a gas mixture for inhalation by the patient,
- allowing the patient to inhale the provided gas mixture via an inlet (21),
30 - passing the gas exhaled by the patient to an outlet (22),
characterized in that said provided gas mixture contains a predetermined set of volatile
organic compounds (VOC) markers.

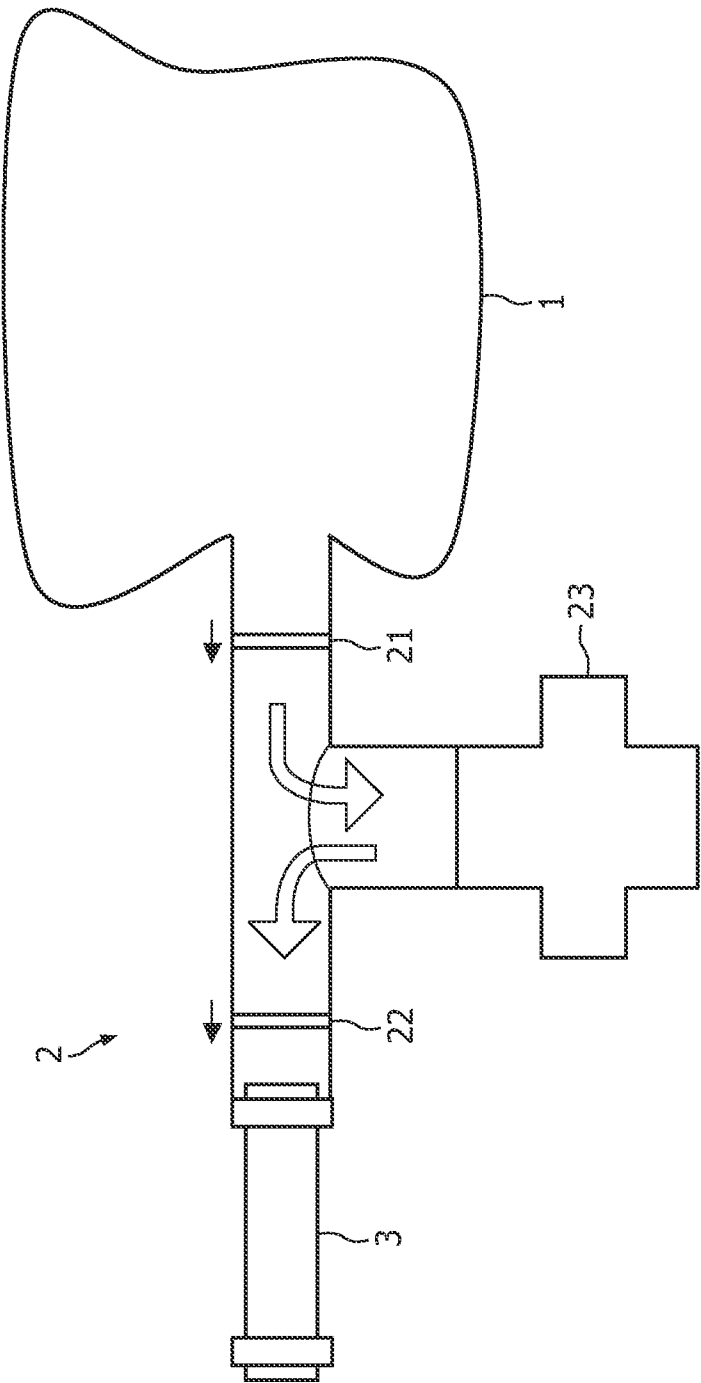


FIG. 1

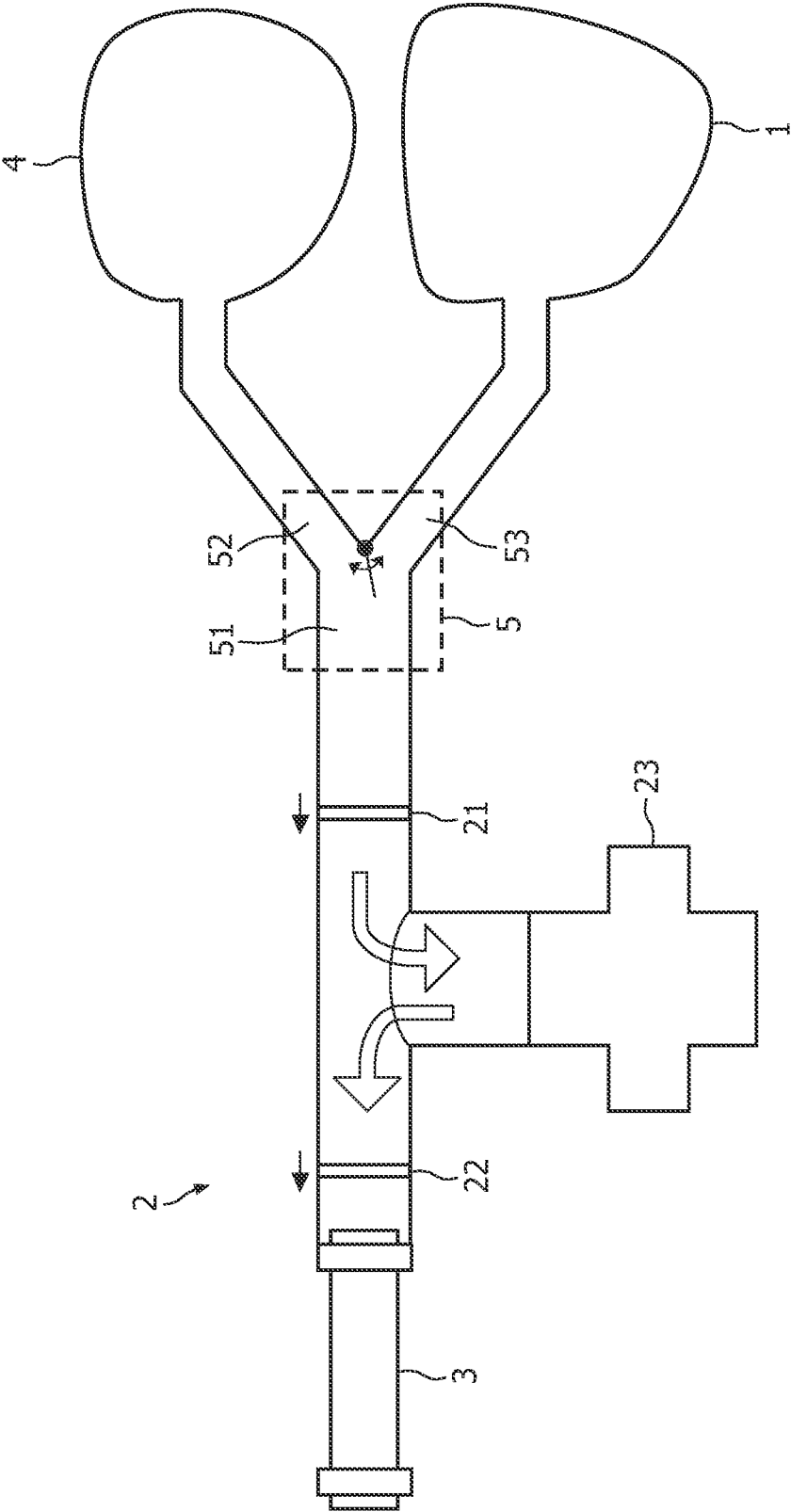


FIG. 2

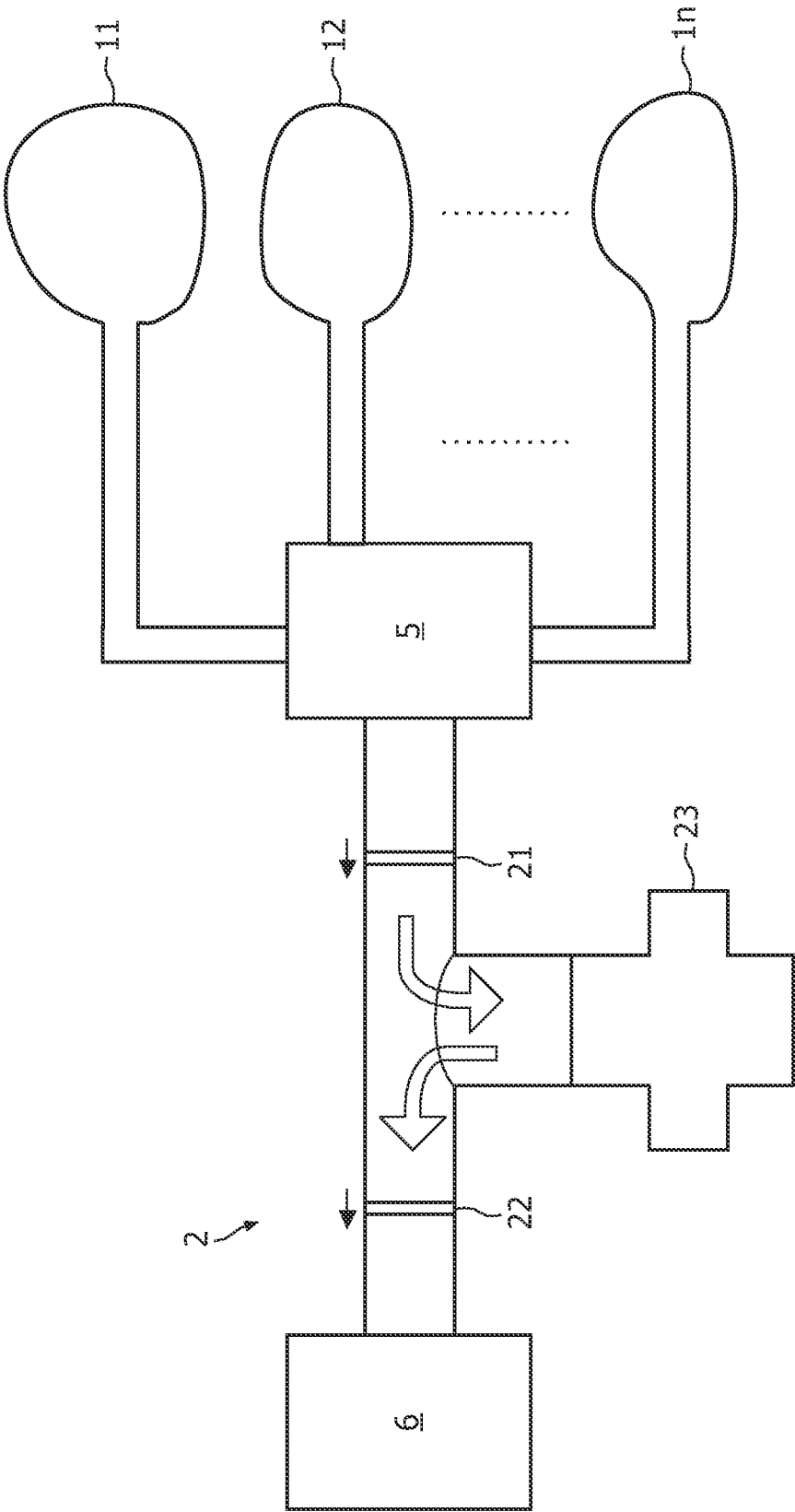


FIG. 3