METHOD AND APPARATUS FOR CHANGING THE BODY TEMPERATURE OF A MAMMAL

Abstract: The present invention relates to an apparatus for increasing or reducing the body temperature of a mammal which forms a closed or substantially closed loop conduit when connected to the airways of said mammal, within which a gaseous heat carrier medium may circulate between the airways of the mammal and a heat exchanger unit. The invention furthermore relates to methods of reducing or increasing the body temperature of a mammal, comprising the steps of administering a gaseous heat carrier medium to the airways of said mammal.
Method and Apparatus for Changing the Body Temperature of a Mammal

FIELD OF THE INVENTION
The present invention is directed to methods and apparatuses for rapidly changing the body temperature of a mammal.

BACKGROUND OF THE INVENTION
Patients undergoing operations that require low blood flow or circulatory arrest often must have their body temperature lowered prior to surgery in order to help protect the heart and brain. In particular, hypothermia has been induced in patients undergoing cardiac surgery and operations for cerebral aneurysms. More recently, the lowering of body temperature has been used as a technique for protecting the brain in cardiac arrest, head trauma and stroke patients and there are indications that this procedure may be useful in treating patients for hemorrhagic shock.

U.S. Patent No. 6,303,156 discloses a method for changing a patient’s body temperature via inhalation of a sulfur hexafluoride-containing gas mixture. However, the use of sulfur hexafluoride is problematic for environmental and economic reasons, since the method as disclosed in U.S. 6,303,156 does not allow a recycling of the heat exchange medium, resulting in a continuous loss of sulfur hexafluoride into the atmosphere. Since sulfur hexafluoride is a rather expensive material as well as one of the most active greenhouse gases, the loss of material is disadvantageous for the reasons as mentioned.

WO 00/18459 discloses a method for inducing hypothermia by employing liquid ventilation of the lungs. This method benefits from the fact that liquids useful for liquid ventilation methods show higher heat capacities than gases, resulting in a more efficient heat exchange. However, the method and apparatus according to WO 00/18459 is rather complicated and requires large volumes of liquids.
US 5,429,123 discloses a heliox ventilation system where helium is used to increase respiration efficiency.

The present invention discloses a method and apparatus that can be used for rapidly inducing hypothermia or, alternatively, for rapidly warming a hypothermic patient that avoid or reduce the loss of heat exchange medium by employing a closed or substantially closed system. A further objective of the present invention is to provide a portable apparatus for the above-mentioned use, which is e.g. suitable for the use in an ambulance or which can be carried to a patient.

SUMMARY OF THE INVENTION

The present invention is directed to an apparatus for increasing, maintaining, or reducing the body temperature of a mammal, which forms a closed or substantially closed loop conduit when connected to the airways of said mammal, within which a heat carrier medium may circulate between the airways of the mammal and a heat exchanger unit, said apparatus comprising a heat exchanger unit and ventilating means for effecting or maintaining circulation of said heat carrier medium between the mammal and the heat exchanger unit.

Another aspect of the present invention relates to an apparatus for increasing, maintaining, or reducing the body temperature of a mammal by administration of a heat carrier medium, comprising

a delivery unit for providing the heat carrier medium to the mammal from a loop conduit within the apparatus and for retrieving the heat carrier medium from the mammal and reintroducing it into the loop conduit;
a heat exchanger unit for increasing or decreasing the temperature of the heat carrier medium, which is connected to the delivery unit by means of the loop conduit; and
ventilating means connected to the delivery unit and the heat exchanger unit by means of the loop conduit for establishing or maintaining a flow of the heat carrier medium within the loop conduit.
In another aspect, the present invention provides an apparatus which is technically simplified and which in one embodiment is portable so that it may be used, for instance, in an ambulance and can be operated by medical or paramedic personnel. A portable apparatus according to the invention can also be carried by a doctor or a paramedic to the location where a patient who due to his/her medical condition may benefit from having his/her body temperature reduced is situated, to start cooling immediately and before the patient is transported to the ambulance.

One advantage of a simplified or portable system according to the present invention is that the cooling of the gas does not require large amounts of energy. By incorporating a heat exchanger unit, comprising a vessel containing a coolant (e.g., a cryogenic liquid such as nitrogen or oxygen, or an under ambient temperature compressed liquid, such as carbon dioxide) in the system, the heat carrier medium can be passed through the heat exchanger and cooled by said coolant.

Another advantage of a portable apparatus according to the present invention is the fact that contrary to conventional ventilators, it requires no or only little electrical energy. This is achieved *inter alia* by the provision of a pneumatically driven ventilator, which for instance, employs the pressure of a source of gaseous oxygen.

In another aspect, the present invention provides a method of reducing, maintaining or increasing the body temperature of a mammal, comprising the steps of:

a) administering a gaseous heat carrier medium to the airways of said mammal, the heat carrier medium having a temperature which is lower than (higher than) the body temperature of the mammal;

b) cooling (warming) the heat carrier medium retrieved from the airways of the mammal to the temperature referred to in a) and re-administering the cooled (heated) heat carrier medium to the airways of said mammal.

In another aspect, the present invention relates to the use of the compounds perfluoropropane, perfluorobutane, perfluoropentane, perfluorocyclobutane, or any mixtures thereof, either with one another or with oxygen or an oxygen-containing gas,
for therapeutic purposes, particularly in the context of reducing, maintaining or increasing the body temperature of a mammal.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a flow scheme of an apparatus according to the present invention. Figure 2 shows a flow scheme of another apparatus according to the present invention. Figure 3 shows a flow scheme of a further apparatus according to the present invention.

Figure 4 shows a scheme of a heat exchanger unit suitable for the present invention, which comprises a second vessel (370) containing a second liquid coolant (310), wherein the low temperature is maintained by passing through the second coolant carbon dioxide cooled through adiabatic expansion.

Figure 5 shows a scheme of a counterflow heat exchanger suitable for the present invention, wherein carbon dioxide cooled by adiabatic expansion is used as a coolant.

Figures 6 and 7 show two different operating phases of a pneumatic ventilator unit using pistons (211, 221).

Figure 8 shows a flow scheme of a further apparatus according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

One purpose of the present invention is to provide a simple, non-invasive method and apparatus for rapidly changing the body temperature of a patient. This is accomplished by administering to a patient (i.e., a mammal, preferably a human) a gaseous heat carrier medium.

In one aspect, the invention is directed to a method and apparatus for reducing the body temperature of a patient by administering a gaseous heat carrier medium comprising a pharmaceutically acceptable gas having a density of more than 6 g/L at 0 °C and
atmospheric pressure and a specific heat of at least 0.5 kJ kg\(^{-1}\) K\(^{-1}\) (further referred to herein as “dense gas”). In a preferred embodiment, the dense gas is a perfluorocarbon or a mixture of perfluorocarbons; more preferably, the dense gas is selected from the group consisting of perfluoropropane (C\(_3\)F\(_8\)), perfluorobutane (C\(_4\)F\(_{10}\)), perfluorocyclobutane (C\(_4\)F\(_8\)) and perfluoropentane (C\(_5\)F\(_{12}\)), or any mixture of these gases. Sulphur hexafluoride (SF\(_6\)) can also be used in the apparatus and method of the invention. Particularly preferred are perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane. Depending on how the heat transfer capacities are calculated, it can roughly be said that perfluoropropane has an about 60%, perfluorobutane has an about 160%, perfluorocyclobutane has an about 70%, and gaseous perfluoropentane has an about 200% higher heat transfer capacity than SF\(_6\).

At 0 °C and at 1 atmosphere, C\(_3\)F\(_8\) has a specific heat (c\(_p\)) of 0.74 kJ kg\(^{-1}\) K\(^{-1}\) and a gas density of 8.4 gram/liter; C\(_4\)F\(_{10}\) has a c\(_p\) of 0.95 kJ kg\(^{-1}\) K\(^{-1}\) and a gas density of 10.6 gram/liter; C\(_4\)F\(_8\) has a c\(_p\) of 0.75 kJ kg\(^{-1}\) K\(^{-1}\) and a gas density of 8.9 gram/liter; and gaseous C\(_5\)F\(_{12}\) has a c\(_p\) of 0.95 kJ kg\(^{-1}\) K\(^{-1}\) and a gas density of 12.9 gram/liter. SF\(_6\) has a c\(_p\) of 0.60 kJ kg\(^{-1}\) K\(^{-1}\) and a gas density of 6.5 gram/liter. When considering the parameter molar c\(_p\) which is the specific heat multiplied by the gas molecular weight the values obtained for the gases are as follows: C\(_3\)F\(_8\) = 140 kJ kmol\(^{-1}\) K\(^{-1}\); C\(_4\)F\(_{10}\) = 225 kJ kmol\(^{-1}\) K\(^{-1}\); C\(_4\)F\(_8\) = 150 kJ kmol\(^{-1}\) K\(^{-1}\); and C\(_5\)F\(_{12}\) = 275 kJ kmol\(^{-1}\) K\(^{-1}\). The molar c\(_p\) of SF\(_6\) is 87 kJ kmol\(^{-1}\) K\(^{-1}\).

An advantage according to studies of the above perfluorocarbons over SF\(_6\) is that they have no narcotic effect. They also have a clearly lower impact on global warming compared to SF\(_6\). The particularly preferred perfluorocarbons according to the present invention furthermore partially condensate under certain cooling conditions. Thus, the vaporisation heat can be used to further improve cooling in the lungs of a patient by vaporising a part of the heat carrier medium in the lung.

By adding heavier perfluorocarbons, for instance perfluorohexane, perfluoroheptane, or perfluorooctane, the heat capacity of the heat carrier medium can be even more increased.
If the perfluorocarbons are administered as a liquid phase, it is preferred that the perfluorocarbons are administered in the form of an aerosol comprising droplets of the perfluorocarbons. Preferably, the droplet size is in a range that allows the droplets to enter the lungs of a mammal. More preferably, the average droplet size of the liquid perfluorocarbons is less than ten micrometers.

In a further embodiment, the heat carrier medium additionally comprises one or more gases selected from the group consisting of oxygen, nitrogen, carbon dioxide, carbon monoxide, nitrous oxide, nitric oxide, argon, helium, gaseous hydrocarbons, and xenon.

In order to increase the rate of heat exchange, the heat carrier medium may be administered while the patient hyperventilates, either spontaneously or as the result of mechanical ventilation. When a reduction of the patient's body temperature is desired, the heat carrier medium that is administered must be of a temperature below the body temperature of the patient. Administration is continued until the patient's temperature is reduced to the desired level. Typically, the dense gas may be present in the heat carrier medium at a concentration of between 20 and 80%, the rest of the composition being oxygen, with about an 80% / 20% ratio of dense gas to oxygen being preferred. Unless otherwise indicated, percentages referred to herein indicate mole percent. However, concentrations of the dense gas higher than 80% may occasionally also be useful, e.g., concentrations of 90%, 95%, or higher, as will be explained in more detail below.

The simplest way of achieving hyperventilation is by means of the voluntary cooperation of a patient immediately prior to anesthetization. In patients who are unconscious or anesthetized, hyperventilation may be induced using a standard operating room or ICU ventilator.

It is generally preferred that the pressure of carbon dioxide in the patient's arterial blood be maintained within the normal range while the heat carrier medium is administered. However, recent studies have shown that an increased concentration of CO₂ in the blood (hypercapnia) can contribute to protect the brain from hypoxic-ischemic damage. It might therefore be useful to maintain hypercapnic conditions during treatment in certain situations. This may be done by adding carbon dioxide to
the heat carrier medium. This will be facilitated by the invention if carbon dioxide is
used as a coolant. A carbon dioxide source is thus already available within the
apparatus so that no additional gas source is needed. Thus, the apparatus can be kept
small and is particularly suitable as portable apparatus.

It will be appreciated that hypercapnia, which may be encountered during diving
operations or by patients under general anesthesia with spontaneous breathing, alters
the basic thermoregulatory responses of animals and humans. In animals exposed to
cold, 3-10% inspired CO₂ impairs thermal homeostasis by attenuating shivering and
promoting heat loss through peripheral vasodilation. In a hypercapnia trial in humans
with 4% CO₂ and 20.9% O₂ balance in N₂ it was shown that hypercapnia enhances the
core cooling rate during mild cold stress. This may be attributed in part to a delay in
shivering onset, as well as increased respiratory heat loss during hypercapnic
hyperventilation.

A reduction in body temperature may also be facilitated by maintaining the water
vapour content of the heat carrier medium at low levels, preferably below 10%.
However, a certain content of water vapour is desirable to avoid desiccation of the
patient’s mucous membranes.

The apparatus and method discussed above can, alternatively, be used for increasing
the body temperature of a patient. The same heat carrier medium is administered but,
rather than being cooled prior to administration, it is heated to a temperature above that
of the patient’s body temperature. Again, administration of the heat carrier medium is
maintained until the desired body temperature of the patient is achieved.

Additionally, the apparatus and method described herein may be used for maintaining
isothermia in patients that would benefit from such a treatment. The same heat carrier
medium is administered, the patient’s body temperature is monitored, and the heat
carrier medium is brought to a temperature suitable to maintain a certain desired
patient’s body temperature.
The heat carrier medium administered to the patient may be mixed in a reservoir and then delivered to patients by means of a ventilator of the sort commonly available in hospitals. In procedures designed to lower body temperature, the gas mixture may be forced through a heat exchanger to lower its temperature (see e.g., Beran, et al., J. App. Physiol. 39:337-340 (1975)). In procedures designed to increase body temperature, a heat carrier medium from a mixing reservoir may be delivered using a ventilator, humidified, and warmed by a standard electrically operated heater/humidifier system. As with cooling, warming will be accomplished using a gaseous heat carrier medium as described above. These procedures are merely illustrative and the invention is compatible with any other method for heating or cooling gas mixtures useful as heat carrier media and for effectively delivering them to a patient.

A problem with administering cold dense gases by ventilation can be the high density of the gas. If the patient’s passive recoil of the chest is not strong enough, the efficiency of the cooling is decreased. It is therefore useful in certain situations to use a ventilator that works in both directions, i.e., with both positive and negative pressure. In this case, the gas is first pressed from the first leg of the loop conduit within the apparatus into the lungs with a positive pressure and then sucked out of the lungs into the second leg of the loop conduit with a negative pressure. However, ventilation that operates only with positive pressure is likewise suitable. A chest compression machine can be used for assisting in the emptying of the airways in the expiration phase. Chest compression can also be manually applied by, for instance, the doctor or paramedic personnel.

The monitoring of the patient’s body temperature and blood gas values may be accomplished using procedures that are routine in the art.

The apparatus and method described herein may be used, for example, for cooling patients who have experienced cardiac arrest outside of a hospital. With a portable apparatus according to the present invention, a doctor or a paramedic can start to cool a patient already in his/her home or wherever the cardiac arrest occurred. The portable apparatus or a further apparatus (either portable or not) present in or built into an ambulance will continue the cooling until the patient arrives at the hospital/clinic. The apparatus and method according to the invention can also be used prior to cardiac
surgery or neurosurgery. They may also be used to rapidly lower the body temperature of patients with clinical indications for potential neuro- or tissue protection in-hospital and/or out-of-hospital, e.g. cardiac arrest, myocardial infarction (MI), traumatic brain damage (TBI), anoxic brain injury following resuscitation from prehospital cardiac arrest, severe head injury, hemorrhagic shock, fever, spinal cord injury, treatment of septic shock, ischemic stroke, subarachnoid hemorrhage, perinatal asphyxia, acute liver failure, hepatic encephalopathy, hypoxic-ischemic encephalopathy, viral encephalopathy, status epilepticus, ARDS, ventilator induced lung injury, and the like. As to ARDS, it is noted that perfluorocarbons are known to improve blood oxygenation in ARDS patients (see, e.g., Ragaller et al., Der Anaesthesist, 49 (2000), 291-301; and Beran et al., J. Appl. Physiol. USA 39 (1975), 337-340, the disclosure of both documents being incorporated herein by reference). Thus, administration of a cooled perfluorocarbon-containing heat carrier medium in accordance with the present invention will be particularly useful when lowering the body temperature in ARDS patients.

Additionally, a therapeutic hypothermia may be applied for preparing a patient for surgery and/or during a surgery process, e.g., cardiovascular surgery or neurosurgery. Furthermore, the apparatus and method of the invention may be used in an emergency room setting for rapidly rewarming hypothermic patients, or for a therapeutic hyperthermic treatment in hospital applications, e.g., in the treatment of cancer, such as melanoma, tumours of the head and neck, breast, brain, bladder, cervix, rectum, lung, oesophagus, vulva or vagina; treatment of viral diseases, such as HIV or Hepatitis C; toxic infections; bacterial infections, such as chronic inflammations or ulcerative colitis, Crohn’s disease, pneumonia; bronchial asthma, and the like. In general, the procedures may be performed on all patients for whom body temperature changes are desired (for example body temperature changes in the range of 2-6°C), with the possible exception of patients with asthma. In these patients, there is a risk of inducing bronchospasm and the risk/benefit ratio of using the apparatus and method according to the invention will need to be considered on a case-by-case basis.

As discussed above, the apparatus and method described herein may also be used for maintaining isothermia in a patient that would benefit from such a treatment, e.g., in
hospital applications connected with general surgery such as abdominal surgery or large intestine surgery, cardiovascular surgery such as CAPG surgery or OP-CAB surgery, orthopaedic surgery such as hip replacement or spinal surgery, fever control in neuro or general ICU, and the like.

As mentioned above, one aspect of the present invention relates to an apparatus for increasing, maintaining or reducing the body temperature of a mammal, which forms a closed or substantially closed loop conduit when connected to the airways of said mammal, within which a heat carrier medium may circulate between the airways of the mammal and a heat exchanger unit, said apparatus comprising a heat exchanger unit. When used, the apparatus is combined with conventional ventilating means for effecting or maintaining circulation of said heat carrier medium between the mammal and the heat exchanger unit. Such ventilating means are common medicinal equipment (ventilators) and usually present in a hospital or emergency room setting. An embodiment as described above is preferred for stationary use of the apparatus in a hospital.

In an alternative embodiment, the apparatus of the invention additionally comprises suitable ventilating means for effecting or maintaining circulation of the heat carrier medium between the mammal and the heat exchanger unit. Such an embodiment is preferred for portable apparatuses.

The term “substantially closed” as mentioned above refers to the fact that it may be difficult to connect the airways of the mammal to the loop conduit in a manner that excludes any loss of heat carrier medium, since such a connection may be disturbed, e.g. by movements of the mammal, so that a leakage cannot always be securely excluded. Moreover, it will be understood that the linkage between the mammal and the apparatus cannot be designed in the same manner as the linkages between the other components of the apparatus, since this specific linkage has to connect mechanical means (the delivering unit) and animal tissue.

The term “substantially closed” should furthermore be understood to encompass apparatuses and embodiments of the invention wherein the expired heat carrier medium
is cooled in such a manner that it condenses but that other expired gases like CO₂, oxygen and nitrogen etc. are not condensed. These gases can thereafter be separated from the heat exchange medium in a liquid trap and be released to the atmosphere or into a special vessel adapted therefor. By virtue of the condensation of the heat carrier medium and the removal of unwanted gases like CO₂, the substantially closed loop needs less adsorption material for the adsorption of CO₂. The product life of the apparatus can thereby be increased without changing CO₂ adsorption filters, or in the case of the portable embodiment, it can be made lighter. Another advantage of this solution is that when nitric oxide is added as a medical gas component, the toxic nitrogen dioxide gas NO₂ which is created by the mixing of nitric oxide and oxygen during respiration, will be separated from the heat carrier medium in the liquid trap together with the CO₂ etc. and thereafter be removed from the apparatus. Nitric oxide can thereby safely be added to a cooled patient.

In addition to a heat exchanger unit and ventilating means, the apparatus of the present invention may further comprise an oxygen supply unit, sensor means for determining the concentration of oxygen in the gas mixture, and control means for regulating the dosing unit depending on feedback from the sensor means. The apparatus may further comprise thermosensor means for controlling the temperature of the heat carrier medium before and/or after passage of said medium through the airways of the mammal: It may further comprise control means for regulating the heat exchanger unit depending on the feedback from the thermosensor means. Moreover, it may comprise a heating unit for the regulation of the temperature of the heat carrier medium entering the airways of said mammal. Additionally, the apparatus may comprise a heat carrier medium.

In a preferred embodiment, the heat carrier medium comprises a gas, preferably a gas that is pharmaceutically acceptable and inert, having a density of at least 6 g/L at 0 °C and a specific heat of more than 0.5 kJ kg⁻¹ K⁻¹ at atmospheric pressure; more preferably, the gas is a perfluorocarbon or a mixture of perfluorocarbons; and most preferably, the gas is selected from the group consisting of perfluoropropane, perfluorobutane, perfluorocyclobutane and perfluoropentane, or a mixture of these gases. Most preferably, the dense gas may be present in the heat carrier medium in a
range from 20 mole percent to 80 mole percent. However, for shorter periods the amount of dense gas may exceed the above range (e.g., may be present in the heat carrier medium in amounts higher than 80%, e.g. 90%, 95%, or even higher), if a temporary hypoxic state of the patient is desired. In the application of the apparatuses and methods according to the present invention it may also be advantageous to start the cooling without any oxygen, or only a low concentration of oxygen, in the heat carrier medium, e.g., when the heart is restarted, to avoid reperfusion injuries.

In a preferred embodiment, the heat carrier medium consists of perfluorobutane (C₄F₁₀) and oxygen (O₂).

In another preferred embodiment of the apparatuses, methods, and uses of the invention, the heat carrier medium consists of perfluorobutane (C₄F₁₀), perfluoropentane (C₅F₁₂), and oxygen. In this regard, preferred ranges regarding the individual components are from 20 to 50% per volume O₂, 28 to 70% per volume perfluorobutane (C₄F₁₀), and 10-22% per volume perfluoropentane (C₅F₁₂). A preferred specific mixture for the heat carrier medium to be used in connection with the invention is a mixture of 20% per volume O₂, 70% per volume C₄F₁₀, and 10% per volume C₅F₁₂; also preferred is a mixture of 30% per volume O₂, 55% per volume C₄F₁₀, and 15% per volume C₅F₁₂; or a mixture of 40% per volume O₂, 42% per volume C₄F₁₀, and 18% per volume C₅F₁₂; and a mixture of 50% per volume O₂, 28% per volume C₄F₁₀, and 22% per volume C₅F₁₂.

In a preferred embodiment the heat exchange unit comprises a vessel containing a coolant. In one preferred embodiment, the temperature of said coolant may be reduced through adiabatic expansion of the coolant. The adiabatically expanded coolant may be directly employed as a coolant, or alternatively, it may be used to cool a second liquid coolant in a second vessel comprised in the heat exchanger unit.

A preferred coolant for adiabatic expansion is carbon dioxide (CO₂). If carbon dioxide is used, the vessel for the carbon dioxide may be connected to the loop conduit to allow the introduction of carbon dioxide into the circulation of said heat carrier medium.
Such an embodiment is particularly preferred for the generation of hypercapnia, as mentioned above.

Alternatively, the heat exchanger unit may comprise a counterflow heat exchanger.

In another embodiment, the heat exchanger unit comprises a vessel containing a cryogenic liquid, for example liquid nitrogen, liquid oxygen, liquid argon, liquid helium, or liquid air. The heat carrier medium passing through the heat exchanger unit is cooled by the cryogenic liquid. Also preferred is the use of oxygen as the cryogenic liquid. In this case, the vessel containing the cryogenic liquid may be connected to the loop via an expansion valve, so oxygen that became vaporized during heat exchange is directly added into the heat carrier medium, and the vessel acts as a gas source for oxygen. Such an embodiment is further advantageous, since the vaporized oxygen from the cryogen vessel has a low temperature, resulting in an enhanced cooling effect.

In another embodiment, the heat exchanger unit comprises a Peltier element. Such an embodiment is particularly preferred for apparatuses suitable for both heating and cooling the heat carrier medium, since the change from heating to cooling can simply be performed by changing the polarity of the electric current at the Peltier element.

The ventilating means according to the present invention may comprise a positive pressure ventilator or a positive and negative pressure ventilator, as mentioned above.

In addition to the heat exchanger unit, the apparatus according to the invention may further comprise a heating unit, which allows fine regulation of the temperature of the heat carrier medium that is administered to the patient. Such an embodiment is particularly preferred for apparatuses according to the invention, wherein the heat exchanger unit comprises a vessel containing cryogenic liquids or other types of heat exchanger units which do not allow a regulation of the cooling effect, or allow regulation only to a limited extent.

The heat exchanger unit may be located in the loop conduit in a manner that the heat carrier medium passes the heat exchanger unit directly before administration to the
patient, as shown for example in Figure 1. Alternatively, the heat carrier medium may pass through the heat exchanger unit directly after it is retrieved from the patient’s airways.

When practicing the method of the present invention, or using the apparatus as described herein, it is preferred that the concentrations of oxygen and carbon dioxide in the patient’s blood are continuously monitored during administration of the heat carrier medium to avoid anoxia. Measurements of oxygen and carbon dioxide levels may be performed via several methods. The concentrations may be determined via direct measurement of gas concentrations in the blood, e.g., by pulse oximetry. The oxymetric measurement can be performed in a non-invasive manner by spectroscopic determination of oxyhemoglobin concentration in the blood, e.g., as disclosed in EP-0 524 083-A1 or U.S. 5,413,100, the disclosure of both documents being incorporated herein by reference. Another possibility for oxymetric measurements is the employment of polarographic methods which are well established in the art. Invasive methods which include a step of taking a blood sample are, of course, likewise suitable to determine the concentration of oxygen in the blood. Similarly, the carbon dioxide level in the blood may be determined, i.e., by direct measurements of the gas concentration in the blood. Alternatively, the oxygen and/or carbon dioxide content of the heat carrier medium may be determined by spectroscopic measurements in the medium itself, either before or after its administration to the patient.

The apparatus may further comprise a source of gaseous oxygen, wherein the gaseous oxygen can be in the form of pure or substantially pure oxygen gas, or of an oxygen-containing gas mixture, preferably compressed air. In a preferred embodiment of the invention, the gaseous oxygen is present in the form of compressed pure or substantially pure oxygen, and the pressure of the compressed pure or substantially pure oxygen is used to drive the ventilating means. The term “substantially pure” is meant to comprise oxygen gas containing 89%, preferably 93%, and more preferably 99.5% or more oxygen; particularly preferred is medical grade oxygen.

Additionally, it may further be advantageous to monitor the patient’s blood and/or bladder temperature to ensure efficient and secure operation of the apparatus.
The apparatus according to the present invention may further comprise a gas purifying unit. Suitable gas purifying units may comprise a filter device for removing the expired CO₂ from the heat carrier medium. The filter device may remove the carbon dioxide by physical effects, e.g., by dissolving the CO₂ in a suitable solvent or adsorbing CO₂ on a suitable adsorber material, or by chemical effects, e.g., by reacting the CO₂ with a suitable substrate, e.g., soda lime. Filter devices as described above are known in the art, e.g., molecular separators, gas purifiers or wet gas cleaners may be employed. The removal of CO₂ may either be complete or (if isocapnic or hypercapnic conditions are desired) incomplete. Additionally, the gas purifying unit may comprise further filter systems, e.g., a charcoal filter for removing traces of hydrocarbons expired by the patient, or a particle filter for removing bacteria.

In order to reduce or avoid loss of heat carrier medium during the step of administering the cooled heat carrier medium to a patient, it is preferred that the apparatus according to the present invention further comprises a delivering unit that is capable of forming a closed or substantially closed loop conduit together with the loop conduit of the apparatus when connected to the airways of the patient. The delivery unit serves to provide the heat carrier medium to the airways of the patient, and to retrieve the heat carrier medium again from the airways of the patient. In this way, the heat carrier medium may circulate between the patient’s airways and the heat exchanger unit within the apparatus. Preferred delivery units are an endotracheal tube or a face mask. Such ventilation systems are known in the medical arts, e.g., for administration of anesthetic gases. The use of endotracheal tubes with two conduits further improves the efficiency of the heat exchange. By using such tubes, a continuous flow of heat carrier medium may be achieved. Additionally, the negative impact of tracheal secretion on the flow of the heat carrier medium may be reduced.

To further improve the heat exchange in the lung, the endotracheal tube can be designed as a double tube. One tube can be concentrically enclosed in a second tube, or two substantially parallel tubes can be used. The length and the width of the tubes can then be chosen such that the flow characteristics of the heat carrier medium in the lung is improved. One example is to have a long inlet tube which reaches deeper down in the
lung, and a shorter outlet tube which ends higher up in the lung or in the trachea, causing an effective flow of the heat carrier medium into and out of the lung. The same principle can be used for a tracheostomy tube. When using a nebulizer, an additional tube for the nebulized part of the heat exchange medium can be provided inside or outside any of the two tubes.

In order to reduce or avoid loss of warming/cooling capacity of the heat carrier medium, it is preferred that the tubes that form part of the loop within which the medium circulates are thermally insulated, e.g., by using insulating plastic coatings.

The apparatus according to the invention may further comprise a nebulizer for the administration of a liquid heat carrier medium. Such an administration may be suitable in the case that the cooling rate in the heat exchanger unit is sufficient to cause a partial condensation of the heat carrier medium, particularly the perfluorocarbon compounds, in or after the heat exchanger unit. In that case, the liquid phase may be nebulized into an aerosol, and the aerosol be admixed to the circulating gaseous heat carrier medium. Suitable nebulizers are known in the art. It is preferred that the average droplet size of the nebulized liquid heat carrier medium is less than ten micrometers, since droplets of this size range are particularly capable of entering the lung of a mammal when inhaled.

Alternatively, it may be desirable to support the heat transfer in the patient by additional administration of aerosols comprising perfluorocarbons that are in the liquid phase under normal conditions, but vaporize in the patient’s lungs. Since the vaporization step requires high quantities of energy that are taken from the patient’s body in the form of thermal energy (heat), the corresponding embodiment is preferred for apparatuses providing a particularly strong cooling performance.

The apparatus according to the invention may also comprise means for admixing to the heat carrier medium one or more further gases suitable for medical purposes which are compatible with the heat carrier medium, e.g., nitrogen, carbon dioxide, carbon monoxide, nitrous oxide, nitric oxide, argon, helium, gaseous hydrocarbons, or xenon, and corresponding sources. For example, patients having had cardiac arrest often suffer from hypoxia which can lead to brain damage due to apoplexy (ischemia).
By admixing xenon to the heat carrier medium, which is a known neuroprotector, the damages to a patient can be reduced. It is known in the art that oxygen deficiency in the brain, e.g. in the case of apoplexy (ischemia) causes an increase in neurotransmitter release, which neurotransmitters are able to kill neuronal cells by induction of apoptosis or by forming neurotoxic metabolites (neurointoxications or neuropoisonings). Additionally, such neurointoxications are considered to occur in hypoxia, oxygen deficiency during birth, Parkinson’s disease, craniocerebral trauma, drug abuse, schizophrenia, depressions and Gilles de la Tourette syndrome (see EP-1 158 992-B1 (Petzelt et al.), the disclosure of which is incorporated herein by reference). Use of a heat carrier medium further comprising xenon for administration to a patient suffering from an oxygen deficiency in the brain is preferred, since decreasing the patient’s body temperature reduces the oxygen deficit by lowering the metabolic rate in the tissue, while xenon reversibly suppresses the release of neurotransmitters. Thus, neurointoxication can be avoided or decreased.

By admixing carbon monoxide to the heat carrier medium (either alone or in combination with xenon), which is known to have anti-inflammatory effects, damages to the patient can be further minimised. The anti-inflammatory effect of carbon monoxide may particularly be employed for the treatment of emphysema, bronchitis, adult respiratory distress syndrome, sepsis, cystic fibrosis, pneumonia, interstitial lung diseases, idiopathic pulmonary diseases, pulmonary hypertension, cancer, Parkinson’s disease, Alzheimer’s disease, peripheral vascular disease, pulmonary vascular thrombotic diseases (e.g., pulmonary embolism), sepsis, septic shock, and disease-states characterized by oxidative stress (see, e.g., WO 03/094932 (Choi et al.), the disclosure of which is incorporated herein by reference). Additionally, carbon monoxide is known to be suitable for the treatment of ischemic disorders.

Nitrous oxide can also be admixed, either alone or in combination with any of the above further gases or combinations of gases, to take advantage of its anesthetic or analgesic characteristics.
By introducing nitric oxide, which has known vaso- and bronchodilatory functions, the gas exchange in the lungs and/or the oxygenation of the blood may be further enhanced in individuals suffering from bronchoconstriction or reversible pulmonary vasoconstriction. Thus, the use of a heat carrier medium further comprising nitric oxide is suitable for treating patients suffering, e.g., from acute pulmonary vasoconstriction, such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome (ARDS), acute pulmonary edema, acute mountain sickness, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparinprothrombin reactions, sepsis, asthma, status asthmaticus, or hypoxia, as well as in those cases of chronic pulmonary vasoconstriction which have a reversible component, e.g., resulting from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia (see, e.g., EP-0 560 928-B1 (Zapol et al.), the disclosure of which is incorporated herein by reference).

Admixing helium to the heat carrier medium is likewise an advantageous embodiment of the invention, in that the high thermal conductivity and diffusivity of the helium results in greater inspired gas temperature equalization towards body temperature.

Since one embodiment of the apparatus of the invention comprises a supply vessel of oxygen and a supply vessel of carbon dioxide within the apparatus, the patient can be maintained in hypoxia/hyperoxia and/or hypocapnia/hypercapnia, or any combination thereof, without the need for supply of external oxygen or carbon dioxide. The combination of creating hypothermia and delivering gases or other medicaments to the patient can clearly improve a patient’s chances of surviving a cardiac arrest without or at least with reduced damages due to apoplexy resulting from hypoxia.

The amount of water vapour in the heat carrier medium can be controlled by including a conventional desiccator/humidifier into the circular gas flow within the loop. It is advantageous in this regard to nebulise the water into the heat carrier medium to avoid icing or clogging of the water. The water could for instance be nebulised into the loop.
at a position within the conduit immediately before the delivery unit, e.g., the endotracheal tube where the heat carrier medium is routed into the lungs.

The apparatus according to the invention may further comprise control means for comparing the actual concentrations of the compounds of the heat carrier medium or the actual blood gas concentrations of the patient, and/or temperatures of the heat carrier medium before and after its administration to the patient and/or the body temperature of the patient and/or pressure of the heat carrier medium within the loop with preset desired values. The control means will then cause a dosing unit to regulate the amount of oxygen (and optionally of one or more of the other afore-mentioned further gases) to be fed into the circular flow, and/or to regulate the performance of the heat exchanger unit, and/or to induce the ventilating means to remove a volume of the heat carrier medium from the loop to maintain a pressure value corresponding to the corresponding preset desired value. The control unit may perform a program control, a sensor control, or a combined program/sensor control. Suitable control units comprise, but are not limited to, a conventional CPU (e.g., a discrete comparator, consisting of transistors or OP-amplifiers).

The ventilating means according to the invention may be connected to a buffer vessel in order to allow the system to store an excess of gas removed from the circular flow and optionally reload it when appropriate, thus maintaining a preset desired pressure value without loss of heat carrier medium and without unnecessary consumption of fresh gas. If the system’s pressure is too high, gas will be pumped from the loop into the buffer vessel to reduce pressure in the loop and vice versa. Buffer systems for maintaining a preset pressure level in gas flow systems are known in the art. In addition to the buffer vessel, suitable buffer systems may further comprise gas mains, control valves, manometers and other technical equipment. The term “buffer vessel” should be understood to optionally comprise one or more, or all those components.

Alternatively, or in addition, the system may comprise gas scavenger means, e.g., a tank containing an absorbing medium connected to the loop conduit via a release valve. If a decrease of pressure in the loop is desired, then a determined volume of heat exchange medium may be removed from the circular flow via the release valve. The
absorbing medium ensures that no dense gas will be released from the apparatus and
the loop conduit when a reduction of pressure is performed via the release valve.
Zeolites, silica gel or other absorbing media known in the art may be used for this
purpose.

It will be understood that an apparatus according to the present invention additionally
comprises the technical means necessary for the forming of the loop conduit and the
addition of the optional further means mentioned herein, e.g., tubes, valves, couplings,
connections, and the like.

In a preferred embodiment, the ventilating means is pneumatically driven. More
preferably, the pressure of the oxygen contained in an oxygen gas source, which is
optionally comprised in the apparatus, is employed for driving the ventilating means.
By using the inherent pressure of the oxygen gas source, no additional energy supplies
or devices have to be added to the apparatus according to the invention. By using the
pressure from the oxygen gas source, a ventilator can be designed with one or two
flexible bags, pistons or bellows to create the desired positive and negative pressure. By
virtue of this ventilator, the patient will first be inflated by an inflation bag/piston and
then be deflated by a deflation bag/piston. Other known ventilators which are not
pneumatically driven may also be used as ventilating means, and may again be, for
instance, flexible rubber bag, bellow or piston type ventilators.

It is further preferred that an apparatus for cooling a patient as described above is in a
portable format, e.g., suitable for being stored or installed in an ambulance. The term
“portable” as used herein is intended to comprise an apparatus having a total weight of
50 kg or less, preferably 25 kg, 20 kg, 15 kg, or even 10 kg or less.

Apparatuses and devices for the administration of medical gases to a patient, which
comprise at least two or more units as described above, are commercially available. It
will be understood that such apparatuses and devices may also be used or adapted for
use in the methods or for the purposes described in connection with the present
invention. It will further be understood that the present invention also comprises the use
of devices wherein at least two units as described above are combined into one single
device. For example, a conventional respirator suitable for the present invention may serve as a dosing unit and as a delivering unit, although it is normally understood to be a single apparatus. It will furthermore be understood that the apparatus according to the present invention can be adapted to be used for cooling other cavities of the mammalian body, such as sinuses, the intrathoracic cavity, and the abdominal cavity.

In another aspect, the present invention is directed to a method of reducing the body temperature of a mammal, comprising the steps of:

a) administering a gaseous heat carrier medium to the airways of said mammal, the heat carrier medium having a temperature which is lower than the body temperature of the mammal;

b) cooling the heat carrier medium retrieved from the airways of the mammal to the temperature referred to in a) and re-administering the cooled heat carrier medium to the airways of said mammal.

In another aspect, the present invention is directed to a method of increasing the body temperature of a mammal, said method comprising the steps of:

a) administering a gaseous heat carrier medium to the airways of said mammal, the heat carrier medium having a temperature which is higher than the body temperature of the mammal;

b) heating the heat carrier medium retrieved from the airways of the mammal to the temperature referred to in a) and re-administering the heated heat carrier medium to the airways of said mammal.

In a preferred embodiment, the methods as mentioned above further comprise the steps of:

c) removing carbon dioxide from the heat carrier medium retrieved from the airways of the mammal; and

d) adding oxygen to the heat carrier medium re-administered to the airways of the mammal.

The steps of removing the carbon dioxide and adding the oxygen may be introduced between or after the previously mentioned steps a) and b), as appropriate.
It will be appreciated that preferred gaseous heat carrier media to be used in connection with the afore-mentioned methods of reducing or increasing the body temperature of a mammal are again those described more specifically above and referred to hereinafter in connection with the apparatus claims.

In a preferred embodiment, the mammal treated by the methods according to the invention is a human. Uses in the area of veterinary medicine are, however, likewise contemplated.

In another embodiment according to the present invention, the method may be performed under hypercapnic conditions. In order to maintain hypercapnic conditions, it is preferred that carbon dioxide is introduced into the heat carrier medium. Said carbon dioxide may be supplied from the heat exchanger unit of an apparatus as described above, if adiabatically expanded carbon dioxide is employed as a coolant.

In another embodiment of the method according to the present invention, the degree of heat exchange is sufficient to partially condense the heat carrier medium, resulting in the generation of a liquid phase of the heat carrier medium. Said liquid phase may be co-administered to the mammal together with the heat carrier medium and vaporize in the airways of the mammal, resulting in a highly efficient heat uptake.

The method described and claimed herein may be applied to patients showing spontaneous breathing or to patients in need of artificial breathing.

Yet a further aspect of the present invention is the use of any of the gaseous heat carrier media as described above and in the context of the apparatuses and methods as claimed hereinafter for reducing, maintaining or increasing the body temperature of a mammal, particularly their use in any of the methods for reducing, maintaining or increasing the body temperature of a mammal described and claimed herein. Also an aspect of the present invention is the use of individual parts or constituents of the apparatuses described and claimed herein in a method for reducing or increasing the body temperature of a mammal, in particular their use in a method as described above and claimed hereinafter. Such parts or constituents include heat exchanger units as
described herein (such as those shown in Figures 1, 3, 4 and 5); ventilating means as
described herein (such as those shown in Figures 1, 2, 3, 6, and 7); delivery units as
described herein; sensor means as described herein (such as the sensor means shown in
Figure 3); oximeters as described herein (such as the oximeter shown in Figure 3);
control means as described herein (such as the control means shown in Figure 3);
heating units as described herein (such as the heating unit shown in Figure 3); buffer
vessels as described herein (such as the vessel shown in Figure 3); gas purifying units
as described herein; sources of carbon dioxide, oxygen, or the further gases as
described herein, e.g., cylinders, cartridges, and the like containing such gases; gas
scavenger means as described herein; coolants and coolant sources as described herein
(such as those shown in Figures 4 and 5); and desiccators/humidifiers, in particular
when the afore-mentioned parts or constituents are specifically adapted for use in any
of the methods and apparatuses described and claimed herein. Such parts or
constituents also include tubing, adapters, connections, couplings, manometers, gas
mains, valves, such as control valves, bags, pistons, bellows, and the like, in particular
when specifically adapted for use in any of the methods and apparatuses described and
claimed herein.

The method for increasing, maintaining or decreasing the body temperature of a
mammal according to the invention may be used in combination with other heating or
cooling methods known in the art. For example, the patient may additionally be cooled
by using cooling blankets or placing the patient in a cooling bath. Additional infusions
with cooled saline solution are also possible and will result in a rapid decrease of the
body temperature; the lower temperature level may then be stabilized by applying the
methods or apparatuses of the invention.

In this regard, a preferred embodiment of any apparatus described and claimed herein
further comprises a storage unit for storing a cooled liquid, e.g., a cooled saline solution
for rapid or additional cooling according to the method discussed above. The storage
unit can then utilise the cooling function of the apparatus to become or remain cool.
The storage unit may be thermally insulated to further improve the cooling efficiency.
For instance, in the embodiment wherein the apparatus is portable, a patient can easily
be given a cold infusion by using the cooled saline solution incorporated into the storage unit of the apparatus.

The method for increasing, maintaining or decreasing the body temperature of a mammal according to the invention is further suitable for a selective temperature control of certain organs of a patient. For example, administration of the heat carrier medium to the lungs of a patient may be applied for a selective cooling/heating of the patient’s thoracic region, while nasal administration of the heat carrier medium may result in a selective cooling of the sinus cavities in the patient’s head, thus leading to rapid cooling of the patient’s head and/or neck. For selective temperature control, the method according to the invention is preferably combined with further methods of temperature control as discussed above. For example, application of warming blankets to the limbs of a patient may be advantageous, if selective cooling of the thoracic region is preferred.

EXAMPLES

Example 1

As can be seen from the example shown in Figure 2, liquid heat carrier medium is transported either with a ventilator (4) or through spontaneous breathing, into a nebulizer (3) where the liquid heat carrier medium is nebulized to an aerosol and introduced into a patient, the exhalation is carried out into a flexible bag (1) to avoid barotrauma which otherwise could occur through the expansion of the heat carrier medium due to vaporization of the aerosol in the lung. The mixture from the flexible bag (1) enters a liquid trap (2) and is cooled so that the heat carrier medium is condensed whereas the other gases like nitrogen, carbon monoxide and excessive oxygen etc. are separated. Also water, which will freeze in the liquid trap (2), can be separated from the heat carrier medium. The liquid heat carrier medium, now substantially free from impurities consisting of other gases, is then transported from the liquid trap into the substantially closed loop to enter the nebulizer (3) and thereafter the patient (5). This setup is especially advantageous when the heat carrier medium consists of, or comprises,
perfluoropentane which can easily be separated in the liquid trap and then later nebulized in the nebulizer.

Means for pumping the expired gases and the condensed heat carrier medium will advantageously be incorporated in most cases. A buffer vessel for the condensed heat carrier medium and a heat exchanger for bringing the heat carrier medium to the desired temperature before entering the nebulizer or the patient may also be incorporated. In a special embodiment according to this example, the heat carrier medium substantially consists of a mixture of perfluoropentane and perfluoropropane. Both PFCs will be cooled and will condense in the liquid trap. This means that the temperature in the liquid trap has to be below the boiling point of the perfluoropropane. The liquid heat carrier medium is then pumped to a heat exchanger where the temperature is increased to the desired temperature for entering into the patient. The heat exchanger medium now has a liquid, perfluoropentane, and a gaseous, perfluoropropane, phase. In the buffer vessel, the phases can be separated. Depending on the cooling needs of the patient, liquid perfluoropentane can be fed to the nebulizer at the same time as gaseous perfluoropropane is fed directly to the patient. For other cooling conditions, only the liquid perfluoropentane is fed to the nebulizer or only the gaseous perfluoropropane is fed to the patient from the buffer vessel. With the same setup, a patient can first be cooled with nebulized perfluoropentane and cold perfluoropropane gas, and later, if necessary, be heated with a warm mixture of perfluoropentane and perfluoropropane, which has been heated in the heat exchanger.

Example 2

An illustrative example of an apparatus according to the invention is shown in Figure 3, wherein the apparatus comprises gas sources for oxygen (11), octafluoropropane (12) and an optional further medical gas (13), which are connected to the loop conduit via a control valve (70). The circular loop comprises a ventilating means (20), a heat exchanger unit (30), a delivering unit for administering the gas mixture to the patient and retrieving it again from the patient to reintroduce it into the circular flow (not reproduced in Figure 3), one or several gas purifying unit(s) (40) for removal of carbon dioxide expired by the patient and contained in the exhaled heat carrier medium (and optionally removal of other impurities, e.g., water vapour or traces of other metabolic
gases), thermosensor units (51, 52, 53) for the measurement of the gas temperature before and after passage through the airways of the patient as well as for the measurement of the patient's body temperature, an oxymeter (60) for measuring the content of oxygen in the heat carrier medium after removal of the carbon dioxide, and the control valve (70) for regulating the gas input from the gas sources into the flow of the heat carrier medium. The composition of the fresh gas input is regulated by the valves (71), (72) and (73). The ventilating means (20) is optionally connected to a buffer vessel (80) in order to allow the system to store excess gas from the circular flow and optionally reload it. (It will be understood that the presence of such a buffer vessel requires the presence of a system of gas mains, manometers and control valves for the connection between the ventilating means (20) and the buffer vessel (80), which are not reproduced in the Figure). The information regarding gas concentrations, pressures, and temperatures of the heat carrier medium is collected by the control unit (90), which regulates the performance of the ventilating means (20) and the heat exchanger unit (30) and controls the input of fresh gas via the control valve (70) and the composition of the fresh gas by the valves (71), (72) and (73). A heating unit (35) may optionally be employed for fine regulation of the temperature of the heat carrier medium.

Example 3

An illustrative example of a pneumatic ventilating means suitable for the present invention is given in Figures 6 and 7. In the expiration phase (Figure 6) the ventilation means sucks in heat carrier medium containing dense gas and O₂ that is exhaled by the patient and passed through a CO₂ absorption device (not shown in Figure 6). The suction pressure is induced by pressurized oxygen from an oxygen source (280) filling a small vessel (210). The second vessel (220) into which the expired heat carrier medium is sucked has a volume corresponding to a little less than one breath. The vessel (210) has a volume appropriate to contain an amount of oxygen equal to or higher than the amount normally needed to compensate for the oxygen consumed by the patient. The pistons (211) and (221) of both vessels (210) and (220) are connected via the linkage (230). In case a higher oxygen concentration is required the pressure of the oxygen filling the smaller vessel is increased. In the inspiration phase (Figure 7) the vessels (210, 220) are emptied by the virtue of the force of the spring (240) that was compressed by the oxygen pressure in the expiration phase. Oxygen is mixed with the
heat carrier medium pressed out of the bigger vessel (220) via adjustable flow restrictors (valves) (250, 260) and fed into the heat exchanger (not shown in Figure 7). A small amount of dense gas, corresponding to leakage losses, is added from the storage (270) or source to the heat carrier medium.

Example 4

An illustrative example for a heat exchanger unit suitable for the purposes of the present invention is given in Figure 4. Acetone (310) or another suitable liquid substance is used as liquid secondary coolant. The secondary coolant is cooled by using the latent heat of compressed, ambient temperature liquid CO₂ in a vessel (320). Expanding the compressed CO₂ through the valve (340) from, e.g., 60 bar/20°C to 7 bar gives a -50°C mixture of gas and liquid phase CO₂ that is used for cooling the acetone which in turn cools the heat carrier medium (330). Evaporation of the liquid phase CO₂ at -50°C at a supply rate of, e.g., 35g/min requires on average an equal amount of energy to be removed from 40 liter/min of heat carrier medium to cool it from 20°C to -10°C. The design of Figure 4 ensures a smooth temperature control. The acetone may be maintained at a temperature of, e.g., -20°C by regulating the flow of CO₂ to the second vessel (370). The valve (350) downstream of the heat exchanger unit is controlling the pressure of CO₂, before the CO₂ is further expanded to ambient pressure. The pressure of the CO₂ passing through the second vessel (370) should preferably be maintained above 7 bar to avoid ice formation and plugging of the gas channel. By increasing the CO₂ flow rate by a factor of five, e.g. from 35 g/min to 175 g/min, a cooling down period of three to four minutes may be achieved. The cooled heat carrier medium can be humidified by the nebulizer (360).

Example 5

An illustrative example of a counterflow heat exchanger unit suitable in the context of the present invention is given in Figure 5. In this embodiment the heat carrier medium (330) is cooled in an annular tube (380). As in the previous example, the cooling capacity of adiabatically expanded carbon dioxide from a vessel (320) is employed. The CO₂ is supplied to the inner tube (381) of the annular tube via the expansion valve (340), and the flow of the heat carrier medium (330) into the external tube (382) of the annular tube (380) is made counter-current. The CO₂ consumption may be reduced,
e.g., to 30g/min, compared to the exemplary rates shown in the embodiment of Figure 4. As in the previous design, the cooled medium may be humidified by a nebulizer (360).

Example 6

Example 6 specifies representative pure perfluorocarbon compounds suitable for the purposes of the present invention by their chemical formulae and boiling points.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Boiling temperature at 1 atm, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{3}F\textsubscript{8}</td>
<td>-36,7</td>
</tr>
<tr>
<td>C\textsubscript{4}F\textsubscript{8}</td>
<td>-5,8</td>
</tr>
<tr>
<td>C\textsubscript{4}F\textsubscript{10}</td>
<td>-2,0</td>
</tr>
<tr>
<td>C\textsubscript{5}F\textsubscript{12}</td>
<td>+30</td>
</tr>
<tr>
<td>C\textsubscript{6}F\textsubscript{14}</td>
<td>+56</td>
</tr>
<tr>
<td>C\textsubscript{7}F\textsubscript{16}</td>
<td>+80</td>
</tr>
<tr>
<td>C\textsubscript{8}F\textsubscript{18}</td>
<td>+97</td>
</tr>
</tbody>
</table>

Example 7

Example 7 lists specific compositions comprising perfluorocarbon compounds that are suitable as heat carrier media in the present invention.

<table>
<thead>
<tr>
<th>O\textsubscript{2} (Vol %)</th>
<th>C\textsubscript{4}F\textsubscript{10} (Vol %)</th>
<th>C\textsubscript{5}F\textsubscript{12} (Vol %)</th>
<th>Relative cooling capacity of gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>70</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>55</td>
<td>15</td>
<td>0,9</td>
</tr>
<tr>
<td>40</td>
<td>42</td>
<td>18</td>
<td>0,8</td>
</tr>
<tr>
<td>50</td>
<td>28</td>
<td>22</td>
<td>0,75</td>
</tr>
</tbody>
</table>
Example 8

A further illustrative example of an apparatus according to the invention is shown in Figure 8. As will be apparent from the Figure, this embodiment comprises a closed loop conduit within which the heat carrier medium may circulate. The heat carrier medium comprises a perfluorocarbon, which is converted into a gaseous phase in the evaporator and introduced into the conduit and mixed with oxygen or an oxygen containing gas. Means for temperature measurement and control (TIC), and for measuring pressure (PI), \( \text{O}_2 \) concentration, and \( \text{CO}_2 \) concentration are likewise advantageously comprised within the apparatus, and optionally connected to a control unit.

The apparatus further comprises a freezing scavenger unit for converting components of the heat carrier medium to the liquid phase and collecting these components. A condensation trap may also be provided to ensure that the heat carrier medium, which enters the cooler is free of any liquid phase.
Claims:

1. Apparatus for increasing, maintaining or reducing the body temperature of a mammal, which forms a closed or substantially closed loop conduit when connected to the airways of said mammal, within which a heat carrier medium may circulate between the airways of the mammal and a heat exchanger unit (30), said apparatus comprising a heat exchanger unit (30).

2. Apparatus according to claim 1, further comprising ventilating means (20) for effecting or maintaining circulation of said heat carrier medium between the mammal and the heat exchanger unit.

3. Apparatus for increasing, maintaining or reducing the body temperature of a mammal by administration of a heat carrier medium, comprising a loop conduit in which the heat carrier medium may flow; and a heat exchanger unit (30) for increasing or decreasing the temperature of the heat carrier medium.

4. Apparatus according to claim 3, further comprising ventilating means (20) connected to the heat exchanger unit by means of the loop conduit for establishing or maintaining a flow of the heat carrier medium within the loop conduit.

5. The apparatus of claim 4, further comprising a delivery unit for providing the heat carrier medium to the airways of the mammal from the loop conduit within the apparatus and for retrieving the heat carrier medium from the airways of the mammal and reintroducing it into the loop conduit, wherein the ventilating means (20) are furthermore connected to the delivery unit by means of the loop conduit for establishing or maintaining a flow of the heat carrier medium within the loop conduit.
6. Apparatus according to any one of the preceding claims, further comprising a gaseous heat carrier medium.

7. Apparatus according to any one of the preceding claims, further comprising an oxygen supply unit connected to the loop conduit, sensor means for determining the concentration of oxygen in the heat carrier medium, and control means for regulating the supply of oxygen depending on feedback from the sensor means.

8. Apparatus according to any one of the preceding claims, further comprising thermosensor means to measure the body temperature and/or the temperature of the heat carrier medium before and/or after passage of said medium through the airways of the mammal, control means for regulating the heat exchanger unit depending on the feedback from the thermosensor means, and/or a heating unit for regulating the temperature of the heat carrier medium entering the airways of said mammal.

9. Apparatus according to any one of the preceding claims, wherein the heat carrier medium comprises a dense gas having a gas density of more than 6 gram/liter and a specific heat of at least 0.5 kJ kg$^{-1}$ K$^{-1}$ at atmospheric pressure and 0°C.

10. Apparatus according to claim 9, wherein the dense gas is a perfluorocarbon or a mixture of perfluorocarbons.

11. Apparatus according to claim 9 or 10, wherein the dense gas is selected from the group consisting of perfluoropropane, perfluorobutane, perfluoropentane and perfluorocyclobutane, or any mixture thereof.

12. Apparatus according to claim 11, wherein the heat carrier medium further comprises one or more gases selected from the group consisting of oxygen, nitrogen, carbon dioxide, carbon monoxide, nitric oxide, nitrous oxide, argon, helium, gaseous hydrocarbons, and xenon.
13. Apparatus according to any one of claims 9 to 12, wherein the dense gas is present in the heat carrier medium in a range from 20 mole percent to 80 mole percent.

14. Apparatus according to any one of the preceding claims, wherein the heat exchanger unit comprises a vessel containing a coolant.

15. Apparatus according to claim 14, wherein the heat exchanger unit is designed to allow the reduction of the temperature of the coolant through adiabatic expansion of the coolant.

16. Apparatus according to claim 15, wherein the heat exchanger unit is designed to allow the coolant to cool a second liquid coolant in a second vessel comprised in the heat exchanger unit.

17. Apparatus according to any one of claims 14 to 16, wherein said coolant is carbon dioxide.

18. Apparatus according to claim 17, wherein said vessel containing the carbon dioxide is connected to the loop conduit to allow the introduction of carbon dioxide into the heat carrier medium.

19. Apparatus according to claim 14, wherein the coolant is a cryogenic liquid selected from the group consisting of nitrogen, oxygen, argon, air or helium.

20. Apparatus according to claim 19, wherein the cryogenic liquid is oxygen and wherein the vessel containing the cryogenic liquid is connected to the loop to allow the introduction of vaporized oxygen into said heat carrier medium.

21. Apparatus according to any one of claims 1 to 15 or 17 to 20, wherein the heat exchanger unit is a counterflow heat exchanger unit.
22. Apparatus according to any one of the preceding claims, wherein the ventilating means comprise a positive pressure ventilator.

23. Apparatus according to any one of claims 1 to 21 wherein the ventilating means comprise a positive and negative pressure ventilator.

24. Apparatus according to any one of the preceding claims, further comprising a source of gaseous oxygen.

25. Apparatus according to claim 24, wherein the gaseous oxygen is in the form of pure or substantially pure oxygen gas, or of an oxygen-containing gas mixture, preferably compressed air.

26. Apparatus according to claim 24, wherein the gaseous oxygen is in the form of compressed pure or substantially pure oxygen, and wherein the ventilating means are designed so that the pressure of the compressed pure or substantially pure oxygen is used to drive the ventilating means.

27. Apparatus according to any one of the preceding claims, which is in a portable format.

28. Apparatus according to any one of the preceding claims, further comprising a nebulizer.

29. Apparatus according to claim 28, wherein the nebulizer is capable of providing a liquid heat carrier medium, preferably the liquid phase of a heat carrier medium as defined in any of claims 9 to 11, as an aerosol suitable for vaporizing in the lungs of a patient upon inhalation, preferably an aerosol having an average droplet size of less than ten micrometers.

30. A method of reducing (or maintaining/increasing) the body temperature of a mammal, comprising the steps of:
   a) administering a heat carrier medium, preferably a gaseous heat carrier
medium, to the airways of said mammal, the heat carrier medium having a temperature which is lower than (the same as/higher than) the body temperature of the mammal;

b) cooling (warming) the heat carrier medium retrieved from the airways of the mammal to the temperature referred to in a) and re-administering the cooled (heated) heat carrier medium to the airways of said mammal.

31. The method according to claim 30, further comprising the steps of:

   c) removing carbon dioxide from the heat carrier medium retrieved from the airways of the mammal; and

   d) adding oxygen to the heat carrier medium re-administered to the airways of the mammal.

32. The use of a perfluorocarbon, either alone or in a mixture with pure or substantially pure oxygen or an oxygen-containing gas, for the preparation of a pharmaceutical composition for reducing, maintaining or increasing the body temperature of a mammal.

33. The use of a perfluorocarbon, either alone or in a mixture with pure or substantially pure oxygen or an oxygen-containing gas, for the preparation of a pharmaceutical composition for treating a mammal having a disease-state selected from the group consisting of cardiac arrest, myocardial infarction (MI), traumatic brain damage (TBI), hemorrhagic shock, fever, spinal cord injury, treatment of septic shock, ischemic stroke, subarachnoid hemorrhage, acute liver failure, hepatic encephalopathy, hypoxic-ischemic encephalopathy, viral encephalopathy, status epilepticus, ARDS, ventilator induced lung injury, and perinatal asphyxia, or a mammal undergoing cardiovascular surgery or neurosurgery.

34. The use of a perfluorocarbon, either alone or in a mixture with pure or substantially pure oxygen or an oxygen-containing gas, for the preparation of a pharmaceutical composition for reducing, maintaining or increasing the body temperature of a mammal having a disease-state selected from the group
consisting of cardiac arrest, myocardial infarction (MI), traumatic brain damage (TBI), hemorrhagic shock, fever, spinal cord injury, treatment of septic shock, ischemic stroke, subarachnoid hemorrhage, acute liver failure, hepatic encephalopathy, hypoxic-ischemic encephalopathy, viral encephalopathy, status epilepticus, ARDS, ventilator induced lung injury, and perinatal asphyxia, or a mammal undergoing cardiovascular surgery or neurosurgery.

35. The use according to any one of claims 32 to 34, wherein the perfluorocarbon is selected from the group consisting of perfluoropropane, perfluorobutane, perfluoropentane, perfluorocyclobutane, or any mixtures thereof.

36. The use according to any one of claims 32 to 35, wherein one or more additional medical gases are admixed to the perfluorocarbon.

37. The use according to claim 36, wherein the additional medical gas is selected from the group consisting of oxygen, nitrogen, carbon dioxide, carbon monoxide, nitric oxide, nitrous oxide, argon, helium, gaseous hydrocarbons, and xenon, or any mixtures thereof.

38. The method according to claim 30 or 31, or the use according to any one of claims 32 to 37, wherein the mammal is spontaneously breathing or artificially breathing.

39. The method according to any one of claims 30, 31 or 38, or the use according to any one of claims 32 to 37, wherein the mammal is a human having a medical condition for which neuroprotection or tissue protection is indicated.

40. The method according to claim 39, wherein the medical condition is selected from the group consisting of cardiac arrest, myocardial infarction (MI), traumatic brain damage (TBI), hemorrhagic shock, fever, spinal cord injury, treatment of septic shock, ischemic stroke, subarachnoid hemorrhage, acute liver failure, hepatic encephalopathy, hypoxic-ischemic encephalopathy, viral encephalopathy, status epilepticus, ARDS, ventilator induced lung injury, or
perinatal asphyxia.

41. The method according to claim 39, wherein the human is undergoing cardiovascular surgery or neurosurgery.

42. The method according to any one of claims 30, 31, or 38 to 41, or the use according to any one of claims 32 to 39, wherein the heat carrier medium is cooled by a coolant in a heat exchanger unit.

43. The method according to any one of claims 30, 31, or 38 to 42, or the use according to any one of claims 32 to 39, wherein the mammal is kept at, or transferred into, a hypercapnic state.

44. The method or the use according to claim 43 wherein the mammal is kept at, or transferred into, a hypercapnic state, said hypercapnic state is maintained or achieved by introducing carbon dioxide to the heat carrier medium administered to the airways of said mammal, and wherein the carbon dioxide is supplied by the heat exchanger unit.

45. A method according to any one of claims 30, 31, or 38 to 44, or the use according to any one of claims 32 to 39, or 42 to 44, wherein the heat carrier medium is partially condensed to a liquid phase in the heat exchanger unit to form a liquid phase, and wherein said liquid phase of the heat carrier medium is vaporized in the airways of the mammal.

46. The method or the use according to claim 45, wherein the vaporization heat is used to improve the cooling of the lungs.

47. The method or the use according to claim 45 or 46 wherein the liquid is administered in the form of an aerosol.

48. The method or the use according to claim 47 wherein the droplets of the aerosol have an average size of less than ten micrometers.
49. Perfluoropropane, perfluorobutane, perfluoropentane, perfluorocyclobutane, or any mixtures thereof, either with one another or with oxygen or an oxygen-containing gas, for use in therapy.

50. Perfluoropropane, perfluorobutane, perfluoropentane, perfluorocyclobutane, or any mixtures thereof according to claim 49 for the use specified therein, wherein the use is for reducing or increasing the body temperature of a mammal.

51. A composition comprising a dense gas having a gas density of more than 6 gram/liter and a specific heat of at least 0.5 kJ kg\(^{-1}\) K\(^{-1}\) at atmospheric pressure and 0°C, and another gas selected from the group of gases consisting of nitrogen, carbon dioxide, carbon monoxide, nitric oxide, nitrous oxide, argon, helium, gaseous hydrocarbons, xenon, and any mixtures thereof, for use in therapy.

52. A composition as defined in claim 51, wherein the dense gas is a perfluorocarbon.

53. The use of a perfluorocarbon, either alone or in a mixture with pure or substantially pure oxygen or an oxygen-containing gas, for the preparation of a pharmaceutical composition for reducing, maintaining or increasing the body temperature of a mammal by a method according to any one of claims 30, 31, or 38 to 48.

54. The composition of claim 52 for the use specified therein, or the use of claim 53, wherein the perfluorocarbon is selected from the group consisting of perfluoropropane, perfluorobutane, perfluoropentane, perfluorocyclobutane, or any mixtures thereof.

55. The composition of claim 52 or 54 for the use specified therein, or the use of claim 53 or 54, wherein one or more additional medical gases are admixed to
the perfluorocarbon.

56. The composition or the use of claim 55, wherein the additional medical gas is selected from the group consisting of oxygen, nitrogen, carbon dioxide, carbon monoxide, nitric oxide, nitrous oxide, argon, helium, gaseous hydrocarbons, and xenon, or any mixtures thereof.

57. A method of preparing an inhalable pharmaceutical composition via mixing of a dense gas having a gas density of more than 6 gram/liter and a specific heat of at least 0.5 kJ kg$^{-1}$ K$^{-1}$ at atmospheric pressure and 0°C with pure or substantially pure oxygen or an oxygen containing gas.

58. The method of claim 57, wherein the dense gas is a perfluorocarbon, preferably a perfluorocarbon selected from the group consisting of perfluoropropane, perfluorobutane, perfluorpentane, perfluorocyclobutane, or any mixtures thereof.

59. The method of claim 57 or 58, further comprising admixing one or more additional medical gases to the dense gas, the perfluorocarbon, or the mixture of perfluorocarbons, preferably an additional medical gas selected from the group consisting of nitrogen, carbon dioxide, carbon monoxide, nitric oxide, nitrous oxide, argon, helium, gaseous hydrocarbons, and xenon, or any mixtures thereof.

60. The method according to any one of claims 57 to 59, wherein the dense gas, the perfluorocarbon, or the mixture of perfluorocarbons is in a liquid phase, preferably in the form of an aerosol.

61. The method according to any one of claims 57 to 59, wherein the dense gas, the perfluorocarbon, or the mixture of perfluorocarbons is in a gaseous phase, the method optionally further comprising the step of admixing a liquid heat carrier medium to the dense gas, the perfluorocarbon, or the mixture of perfluorocarbons, the liquid heat carrier medium preferably being in the form of
an aerosol.

62. The method of claim 60 or 61, wherein the aerosol is suitable for vaporizing in the lungs of a patient upon inhalation of the pharmaceutical composition, the aerosol preferably having an average droplet size of less than ten micrometers.

63. The method according to claims 61 or 62, wherein the liquid heat carrier medium is the liquid phase of a heat carrier medium as defined in any of claims 9 to 11.
Figure 1

Loop Conduit for Heat Carrier Medium
Figure 2

Water → Liquid trap (2) → Flexible bag (1) → Patient → Nebulizer (3) → Ventilator (4) → O₂/Air

N₂, O₂, CO₂ etc.