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(54) Title: TRANSPULMONARY SYSTEMIC COOLING USING LIQUID MISTS

(57) Abstract: A method for transpulmonary cooling by providing a liquid having a boiling point of 38 - 300°C, more preferably 38 - 250°C, more preferably 38 - 200°C, more preferably 38 - 150°C, more preferably 38 - 80°C. The liquid is nebulized to form a mist. The mist is optionally cooled below room temperature and delivered to the airway of a patient so that the patient inhales the mist. The mist causes systemic cooling by evaporative heat loss when inhaled at room temperature and additionally by direct heat transfer when inhaled below room temperature. Compositions and medical devices for transpulmonary cooling are also provided.

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TRANSPULMONARY SYSTEMIC COOLING USING LIQUID MISTS

Cross-Reference to Related Application

This application claims the benefit pursuant to 35 U.S.C. § 120 of U.S. Application Serial No. 11/003,015, filed December 1, 2004, which is a continuation-in-part of U.S. Application Serial No. 10/792,365, filed March 2, 2004, which claims the benefit pursuant to 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/535,230, filed January 9, 2004. All of the above-identified applications are incorporated herein by reference in their entirety.

Field of the Invention

The invention relates to transpulmonary systemic cooling, and more particularly to transpulmonary systemic cooling using liquids or liquid mists with boiling points above body temperature.

Background

Patients experiencing cardiac arrest, stroke, head trauma, myocardial infarction, aneurysm neurosurgery, cardiac surgery, shock, cardiac ischemia, or cerebral ischemia often suffer from disabilities ranging from transient neurological deficit to irreversible damage (stroke) or death. Cerebral ischemia, i.e., reduction or cessation of blood flow to the central nervous system, can be characterized as either global or focal. Global cerebral ischemia refers to reduction of blood flow within the cerebral vasculature resulting from systemic circulatory failure caused by, e.g., shock, cardiac failure, or cardiac arrest. Within minutes of circulatory failure, tissues become ischemic, particularly in the heart and brain.

The most common form of shock is cardiogenic shock, which results from severe depression of cardiac performance. The most frequent cause of cardiogenic shock is myocardial infarction with loss of substantial muscle mass. Pump failure can also result from acute myocarditis or from depression of myocardial contractility following cardiac arrest or prolonged cardiopulmonary bypass. Mechanical abnormalities, such as severe valvular stenosis, massive aortic or mitral regurgitation, acutely acquired ventricular septal defects, can also cause cardiogenic shock by reducing cardiac output. Additional causes of cardiogenic shock include cardiac arrhythmia, such as ventricular fibrillation.

With sudden cessation of blood flow to the brain, complete loss of consciousness is a sine qua non in cardiac arrest. Cardiac arrest often progresses to death within minutes if active interventions, e.g., cardiopulmonary resuscitation (CPR), defibrillation, use of inotropic agents and vasoconstrictors such as dopamine, dobutamine, or epinephrine, are not undertaken promptly. The most common cause of death during hospitalization after resuscitated cardiac arrests is related to the severity of ischemic injury to the central nervous system, e.g., anoxic encephalopathy. The ability to resuscitate patients of cardiac arrest is related to the time from onset to institution of resuscitative efforts, the mechanism, and the clinical status of the patient prior to the arrest.

Focal cerebral ischemia refers to cessation or reduction of blood flow within the cerebral vasculature resulting in stroke, a syndrome characterized by the acute onset of a neurological deficit that persists for at least 24 hours, reflecting focal involvement of the central nervous system. Approximately 80% of the stroke population is hemispheric ischemic strokes, caused by occluded vessels that deprive the brain of oxygen-carrying blood. Ischemic strokes are often caused by emboli or pieces of thrombotic tissue that have dislodged from other body sites or from the cerebral vessels themselves to occlude in the narrow cerebral arteries more distally. Hemorrhagic stroke accounts for the remaining 20% of the annual stroke population.

Hemorrhagic stroke often occurs due to rupture of an aneurysm or arteriovenous malformation bleeding into the brain tissue, resulting in cerebral infarction. Other causes of focal cerebral ischemia include vasospasm due to subarachnoid hemorrhage from head trauma or iatrogenic intervention.

Current treatment for acute stroke and head injury is mainly supportive. A thrombolytic agent, e.g., tissue plasminogen activator (t-PA), can be administered to non-hemorrhagic stroke patients. Treatment with systemic t-PA is associated with increased risk of intracerebral hemorrhage and other hemorrhagic complications. Aside from the administration of thrombolytic agents and heparin, there are no therapeutic options currently on the market for patients suffering from occlusion focal cerebral ischemia. Vasospasm may be partially responsive to vasodilating agents. The newly developing field of neurovascular surgery, which involves placing minimally invasive devices within the carotid arteries to physically remove the offending lesion, may provide a therapeutic option for these patients in the future, although this kind of manipulation may lead to vasospasm itself.

Cooling has also been shown to be beneficial in patients undergoing neurosurgical procedures for ruptured aneurysms, and in patients undergoing coronary bypass surgery. In such cases, the protection provided is for the brain. Cooling may also be beneficial for myocardial protection during myocardial ischemia. Cooling is also useful in organ preservation for transplantation, such as kidney preservation, "cryopreservation." Previous methods include the use of "PLV" or partial liquid ventilation, whereby a certain volume of cold, liquid PFC is syringed into the lung and then aspirated out, over and over again. See Harris et al., "Rapid (0.5°C/min) minimally invasive induction of hypothermica using cold perfluorochemical lung lavage in dogs," Resuscitation 50 (2001), pp. 189-204. This method, however, requires the patient to be intubated, which in turn requires sedation or anesthesia or a spontaneouosly unconscious patient. This method can be used in the operating room or ICU but not in the field

where patients are neither unconscious nor intubated, nor are many of them sedatable for intubation (stroke, head injury).

In both stroke and cardiogenic shock, patients develop neurological deficits due to reduction in cerebral blood flow. Treatments should include measures to maintain viability of neural tissue, thereby increasing the length of time available for interventional treatment and minimizing brain damage while waiting for resolution of the ischemia. New devices and methods are thus needed to minimize neurologic deficits in treating patients with either stroke or cardiogenic shock caused by reduced cerebral perfusion.

Summary of the Invention

The compositions, methods, and devices described herein have significant and unexpected advantages over earlier attempts for transpulmonary systemic cooling. Earlier attempts suffer from at least four disadvantages. First, the earlier attempts have a tendency to cause air trapping in the lungs, which is harmful. Second, for compounds with low boiling points, explosive evaporation causing barotrauma has proven to be problematic. Third, delivery is problematic with low boiling compounds because they vaporize before reaching the lower airways. Finally, hypoxia has been noted to be a problem with earlier attempts. Hypoxia occurs when a vaporized gas other than oxygen is present in the lungs and dilutes other gasses present in the lungs. When hypoxia occurs, it becomes necessary to increase the inspired oxygen fraction.

The invention relates to methods, devices, and compositions for transpulmonary cooling. The compositions of the invention include liquids having a boiling point of 38 – 300 °C, more preferably a boiling point of 38 – 200 °C, more preferably a boiling point of 60 – 150°C, more preferably a boiling point of 70 – 125°C, more preferably a boiling point of 75 – 110°C, more preferably a boiling point of 60 – 70°C. Compounds having suitable characteristics for use herein include hydrocarbons, fluorocarbons, perfluorocarbons, and

perfluorohydrocarbons. Saline is another example of a substance having suitable characteristics for use herein. As used in this specification, the terms "fluorocarbon," "perfluorocarbon," and "perfluorohydrocarbon" are synonymous. In addition to containing carbon and fluorine, these compounds may also contain other atoms. In one embodiment, the compounds could contain a heteroatom, such as nitrogen, oxygen, or sulfur, or a halogen, such as bromine or chlorine. These compounds may be linear, branched, or cyclic, saturated or unsaturated, or any combination thereof.

In another embodiment, the compounds are highly fluorinated compounds, which are compounds containing at least three fluorine atoms. These highly fluorinated compounds may also contain other atoms besides carbon and fluorine. These other atoms include, but are not limited to, hydrogen; heteroatoms such as oxygen, nitrogen, and sulfur; and halogens such as bromine or chlorine. In one embodiment, the number of the atoms that are not carbon or fluorine comprise a minority of the total number of atoms in the compound. These highly fluorinated compounds may be linear, branched, or cyclic, saturated or unsaturated, or any combination thereof. Examples of these compounds include, but are not limited to, C_4F_9Br (b.p. 43°C), $CF_3CF(CF_3)CF=CF_2$ (b.p. 51°C), $CF_3CF(CF_3)CH=CH_2$,

In another embodiment, the compounds are hydrofluorocarbons, which are compounds where the number of hydrogen atoms exceeds the number of fluorine atoms. These hydrofluorocarbons may also contain other atoms besides hydrogen, carbon, and fluorine. These other atoms include, but are not limited to, heteroatoms such as oxygen, nitrogen, and sulfur and halogens such as chlorine and bromine. For example, hydrofluorcarbons include, but are not limited to, hydrochlorofluorocarbons, more specifically, hydrochlorofluoralkanes. In one embodiment, the number of the atoms other than carbon and fluorine comprise a minority of the total number of atoms in the compound. These hydrofluorocarbons may be linear, branched, or cyclic, saturated or unsaturated, or any combination thereof.

A mixture of two or more highly fluorinated compounds, hydrofluorocarbons, light fluorocarbons, hydrocarbons, fluorocarbons, perfluorocarbons, perfluorohydrocarbons, or any of the above-mentioned compounds may also be used. The mixture may contain any of the previously mentioned compounds in different phases (e.g., one gas, one liquid). The mixture has a boiling point above 37 °C, even though any individual component of the mixture may have a boiling point below 37 °C.

Light fluorocarbons are fluorocarbons that have a boiling point below 37 °C. These light fluorocarbons may also contain other atoms besides carbon, and fluorine. These other atoms include, but are not limited to, hydrogen; heteroatoms such as oxygen, nitrogen, and sulfur; and halogens such as chlorine and bromine. For example, light fluorocarbons include, but are not limited to perfluorobutane and perfluoropentane. In one embodiment, the number of the atoms other than carbon and fluorine comprise a minority of the total number of atoms in the compound. These light fluorocarbons may be linear, branched, or cyclic, saturated or unsaturated, or any combination thereof.

In certain methods, a liquid having a boiling point of 38 – 300 °C, more preferably having a boiling point of 38 – 200 °C, more preferably having a boiling point of 38 – 150 °C, is selected. The liquid is nebulized to form a mist. The droplets preferably range in size from 0.1 – 100 microns, more preferably 1 – 5 microns, more preferably 2 – 4 microns. The mist is optionally cooled below body temperature and delivered to the airway of a patient so that the patient inhales the mist. Inhalation of the mist causes systemic cooling by heat transfer from the lungs to the cooler mist and/or by evaporative heat loss as the mist evaporates. The administration of the liquid is continued until the systemic temperature is reduced to 35 °C or below, more preferably to 34 °C or below, more preferably to 33 °C or below. The rate of cooling can be adjusted by varying the temperature of the inhalate, the concentration of the

responsible compound or compound mixture, the rate of delivery, the particle size, and the percentage of each compound in the mixture.

In other methods, a saline mist is administered with the mist of one, two, or more highly fluorinated compounds, hydrofluorocarbons, light fluorocarbons, hydrocarbons, fluorocarbons, perfluorocarbons, perfluorohydrocarbons, or any of the above-mentioned compounds. Where saline mist is present, this may allow for a reduced amount of highly fluorinated compounds, hydrofluorocarbons, light fluorocarbons, hydrocarbons, fluorocarbons, perfluorocarbons, perfluorohydrocarbons.

In another embodiment, the liquid is administered directly to the patient. In some circumstances, it may not be necessary to nebulize the liquid. For example, in patients already supplied with an endotracheal tube, pure liquid may be introduced with or without the techniques of partial or total liquid ventilation.

In other methods, a pulmonary vasodilator is added to the compositions described in any of the previously described embodiments. Pulmonary vasodilators relax the smooth muscle in the airways. They are mostly adrenergic agents, such as adrenaline (epinephrine) or albuterol. Selective pulmonary vasodilators relax smooth muscle of arteries in pulmonary circulation but not the systemic circulation. Suitable pulmonary vasodilators include nitric oxide (NO) as well as prostaglandins. Nitric oxide may have a mild bronchodilator effect but only a fraction of its effect on the arterial smooth muscle.

Nitric oxide or adrenergic agents, such as adrenaline (epinephrine) or albuterol, may be added in minute doses to the compositions described in any of the previously described embodiments. The NO or other agent is inhaled and acts as a potent pulmonary vasodilator, which improves the rate of action of the cooling mist and counteracts pulmonary vasoconstriction caused by administering cold substances to the lungs. The NO may be included in an amount of about 2 to about 80 parts per million, in other cases in an amount of about 3 to

about 20 parts per million, in other cases in an amount of about 4 to about 10 parts per million, in other cases in an amount of about 5 to about 8 parts per million, in other cases in an amount of about 5 parts per million.

In other methods, an agent that maintains normal cerebral vascular tone, or even a cerebral vasodilator, is administered with the cooling preparation in order to reverse the cerebral vasoconstriction induced by cooling (or, in order to maintain cerebral perfusion at hypothermia) . One example of an agent useful in this method is carbon dioxide. Thus, carbon dioxide can be administered as a gas along with the cooling mist and oxygen in order to maintain cerebral perfusion.. The addition of carbon dioxide reverses the reduction of carbon dioxide caused by hyperventilation that may be needed for cooling. Normally there is about 40 mmHg of carbon dioxide in blood. If the patient hyperventilates, that level will drop and cause cerebral vasoconstriction. By adding CO2 to the inhaled air, CO2 in the blood is restored to 40 mmHg, thus reversing vasoconstriction caused by hyperventilation.

In other methods, administration of cold mists will occur in cycles with intervening cycles of administering another gas, preferably a cold dry gas such as dry air or dry heliox, e.g., a mixture of helium and oxygen. With continuous administration of PFC mist, the gaseous phase in the lungs may become saturated with gaseous PFC, thereby slowing the rate of evaporative heat loss. In order to accelerate the rate of evaporative heat loss, it may be desired to periodically purge the lungs of PFC. This can be done by cycling administration of cold mists with administering another gas, preferably a dry gas such as dry air or dry heliox.

Where cycling is desired, it is recommended that the cycles occur for about 3 seconds or more, in other cases for about 30 seconds or more, in other cases for about one minute or more, in other cases for about two minutes or more, in other cases for about five minutes or more, in other cases for about ten minutes or more, in other cases for about 30 minutes or more. In other cases, depending on the mist used, the cycles occur for about 5 breaths or less, in other

cases for about 10 breaths or less, in other cases for about 50 breaths or less, in other cases for about 100 breaths or less, in other cases for about 200 breaths or less, in other cases for about 500 breaths or less, in other cases for about 1000 breaths or less.

The intervening cycle of dry gas may last for an equal period (e.g., about 3 seconds of cold mist followed by about 3 seconds of dry gas, about 30 seconds of cold mist followed by about 30 seconds of dry gas, about one minute of cold mist followed by about one minute of dry gas, about two minutes of cold mist followed by about two minutes of dry gas, about five minutes of cold mist followed by about five minutes of dry gas, about ten minutes of cold mist followed by about ten minutes of dry gas, about 30 minutes of cold mist followed by about 30 minutes of dry gas, about 5 breaths of cold mist followed by about 5 breaths of dry gas, about 10 breaths of cold mist followed by about 10 breaths of dry gas, about 50 breaths of cold mist followed by about 50 breaths of dry gas, about 100 breaths of cold mist followed by about 100 breaths of dry gas, about 200 breaths of cold mist followed by about 200 breaths of dry gas, about 500 breaths of cold mist followed by about 500 breaths of dry gas) or for a shorter or longer period (about ten minutes of cold mist followed by about two minutes of dry gas).

Medical devices are also provided for transpulmonary cooling. The devices include an inhaler device and a nebulized liquid in the form of a mist, the liquid having a boiling point of 38 - 300 °C, more preferably having a boiling point of 38 – 200 °C, more preferably having a boiling point of 38 – 150 °C. Any of the biocompatible liquids having boiling points within the ranges described herein are suitable for use with the medical devices described herein. The liquid mist may be cooled to below body temperature before delivery. The mist droplets may range in size from 0.1 – 100 microns, more preferably 1 – 5 microns, more preferably 2 – 4 microns.

Detailed Description

The compositions of the invention include liquids having a boiling point above 37 °C and less than or equal to 300 °C, more preferably 38 – 300 °C, more preferably 38 – 200 °C, more preferably 38 – 150 °C, more preferably 38 – 100 °C, more preferably 38 – 80 °C, more preferably 40 – 150 °C, more preferably 40 – 100 °C, more preferably 40 – 75 °C, more preferably 45 – 150 °C, more preferably 45 – 100 °C, more preferably 45 – 75 °C, more preferably 50 – 150 °C, more preferably 50 – 100 °C, more preferably 50 – 75 °C, more preferably 50 – 70 °C. Compounds having suitable characteristics for use herein include, but are not limited to, highly fluorinated compounds, hydrofluorocarbons, hydrocarbons, fluorocarbons, perfluorocarbons, and perfluorohydrocarbons. Suitable biocompatible liquids include perfluorohexane (b.p. 57 °C), perfluorocyclohexane (b.p. 53 °C), and perfluoroethers selected from the group comprising of $(C_3F_7)_2O$ (b.p. 56 °C), $CF_3(OCF_2)_3OCF_3$ (b.p. 59 °C), C_3F_7-O-C_3F_7 (b.p. 57 °C), $(CF_3OCF_2CF_2)_2O$ (perfluorodiglyme, b.p. 66 °C), $CF_3(OCF_2)_3OCF_3$ (b.p. 59 °C), and the hydrofluoroethers$C_4F_9OCH_3$ (b.p. 60 °C), $C_4F_9OC_2H_5$ (b.p. 76 °C), perfluoro(n-butyl)tetrahydrofurane $C_8F_{16}O$ (b.p. 97-107 °C), perfluoro-2-(n-butyl)tetrahyrofurane, perfluoro-3-(n-butyl)tetrahyrofurane, and others. Further valuable highly fluorinated components include mixed fluorocarbon-hydrocarbon diblock compounds such as, for example, $C_nF_{2n+1}C_mH_{2m+1}$ or $C_nF_{2n+1}OC_mH_{2m+1}$.

Moreover, a mixture of two or more fluorocarbons or highly fluorinated compounds, or a mixture of two or more fluorocarbons and hydrofluorocarbons, may also be used, including mixtures of any of the above-identified compounds. The mixture may further include compounds with boiling points below 37 °C, provided the mixture itself has a boiling point that is above 37 °C. For example, a mixture of perfluorohexane (PFH, b.p. 57 °C) and perfluoropentane (PFP, b.p. 29 °C) having a boiling point above 37 °C has suitable properties,

and is within the scope of the present teaching. The proportions of any mixture of compounds may be varied during the procedure to achieve desired boiling point and vapor pressure characteristics. Moreover, the procedure may be commenced with a higher proportion of PFP (b.p. closer to 29 °C), then to maintain the cooling, the composition can be enriched with a greater proportion of PFH (b.p. closer to 50 °C). The proportions may be varied during the procedure by administering different proportions at different time points. Alternatively, or in addition, the composition may be varied automatically as a result of preferential evaporation of the more volatile components in the body.

In certain methods, the liquid may be cooled to below body temperature before delivery. The liquid or liquid mixture may be cooled to 35 °C or below, 30 °C or below, 25 °C or below, 20 °C or below, 15 °C or below, or 10 °C or below. This pre-cooling will promote a more rapid transpulmonary systemic cooling and reduce the total amount of fluorocarbon required to achieve a set amount of cooling.

In a first method, a liquid having a boiling point of 38 – 300 °C, more preferably having a boiling point of 38 – 200 °C, more preferably having a boiling point of 38 - 150 C, is selected. The liquid is nebulized to form a mist. The droplets preferably range in size from 0.1 – 100 microns, more preferably 0.1 – 20 microns, more preferably from 1 – 5 microns, more preferably from 2 – 4 microns. The mist is delivered to the airway of a patient so that the patient inhales the mist. Inhalation of the mist causes systemic cooling by heat transfer from the cooler mist and/or by evaporative heat loss. The volume of liquid administered typically ranges from 1 to 6 liters or more. In some cases, up to 10 and even 20 L may be administered. In other cases, 3 to 4 liters may be administered. In some cases, less than 1 liter of liquid may be administered, for example, 0.75 liters, more preferably 0.5 liters, more preferably 0.1 liters. This is especially the case if the fluorinated compound is not deposited into the lungs. Induction of cooling is rapid, occurring within 1 minute, 2 minutes, 4 minutes, 8 minutes, or over a longer time period

such as under 30 minutes, under 60 minutes, or over 60 minutes ,depending on the composition, volume, and temperature of the mist administered. The administration of the liquid is continued until the systemic temperature is reduced to 35 °C or below, or more preferably to 34 °C or below. Moreover, the cooling can be maintained for a prolonged period, up to 4 hours or more, 8 hours or more, 12 hours or more, 16 hours or more, 24 hours or more, 36 hours or more, or 48 hours or more.

Medical devices are also provided for transpulmonary cooling. The devices include an inhaler device and a nebulized liquid in the form of a mist the liquid having a boiling point of 38 – 300 °C, more preferably having a boiling point of 38 - 200°C, more preferably having a boiling point of 38 - 150°C. Any of the biocompatible liquids having boiling points within the ranges described herein are suitable for use with the medical devices described herein. The liquid mist may be cooled to below body temperature before delivery. In certain cases, the liquid mist is cooled to 35 °C or below, 30 °C or below, 25 °C or below, 20 °C or below, 15 °C or below, or 10 °C or below. The mist droplets may range in size from 0.1 to 100 microns, more preferably from 0.1—20 microns, more preferably from 1 – 5 microns, more preferably from 2 – 4 microns.

The mist may be delivered in a gaseous mixture containing oxygen, for example, 20% oxygen or more, as in inspired air. Alternatively, the mist may be delivered in a gaseous mixture containing increased fractions of oxygen, for example, more than 20% oxygen or more. The remaining inspired gas can include one or more gaseous fluorinated compound (any of those described herein, such as light fluorocarbons, hydrofluorocarbons or hydrochlorofluorocarbons) rather than nitrogen to increase the cooling capacity of the gaseous mixture, thus further reducing the amount of liquid fluorocarbon required. Other possible components of the gaseous mixture include, but are not limited to, nitrogen, CO_2, as present in carbogen, helium, etc. The fluorinated gas might also be SF_6, a substance approved for many other indications in humans.

In another embodiment, the fluorocarbons may be recovered from the expired gas. In some cases, the recovered fluorocarbons may be readministered to the patient. By recirculation, the total volume of fluorocarbon necessary to achieve systemic cooling can be vastly reduced.

Although the foregoing invention has, for the purposes of clarity and understanding, been described in some detail by way of illustration and example, it will be obvious that certain changes and modifications may be practiced which will still fall within the scope of the appended claims. It will also be understood that any feature or features from any one embodiment, or any reference cited herein, may be used with any combination of features from any other embodiment.

What is claimed is:

1. A method for transpulmonary cooling, comprising the steps of:

providing a liquid having a boiling point of 38 – 300 °C;

nebulizing the liquid to form a mist; and

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling.

2. The method of claim 1, wherein the liquid has a boiling point of 38-200 °C.

3. The method of claim 1, wherein the liquid has a boiling point of 38-150 °C.

4. The method of claim 1, wherein the liquid or liquid mist is cooled to below body temperature before delivery.

5. The method of claim 1, wherein the liquid or liquid mist is cooled to 10 °C or less before delivery.

6. The method of claim 1, wherein the liquid comprises at least one highly fluorinated compound.

7. The method of claim 6, wherein the at least one highly fluorinated compound comprises a linear compound.

8. The method of claim 6, wherein the at least one highly fluorinated compound comprises a branched compound.

9. The method of claim 6, wherein the at least one highly fluorinated compound comprises a cyclic compound.

10. The method of claim 6, wherein the at least one highly fluorinated compound comprises a saturated compound.

11. The method of claim 6, wherein the at least one highly fluorinated compound comprises an unsaturated compound.

12. The method of claim 6, wherein the at least one highly fluorinated compound comprises at least one heteroatom.

13. The method of claim 6, wherein the at least one highly fluorinated compound comprises at least one hydrogen.

14. The method of claim 6, wherein the highly fluorinated compound comprises at least one halogen.

15. The method of claim 1, wherein the liquid is a fluorocarbon.

16. The method of claim 6, wherein the highly fluorinated compound is a perfluoroalkane of the formula C_nF_{2n+2}.

17. The method of claim 16, wherein the perfluoroalkane is perfluorohexane.

18. The method of claim 16, wherein the perfluoroalkane is perfluoroheptane.

19. The method of claim 1, wherein the liquid is a hydrocarbon.

20. The method of claim 1, wherein the liquid is a perfluoroether.

21. The method of claim 20, wherein the perfluoroether comprises at least one halogen atom.

22. The method of claim 21, wherein the perfluoroether has the formula $C_nF_{2n+1}OC_nF_{2n}Br$.

23. The method of claim 21, wherein the perfluoroether is $CF_3OCF_2CF_2OCF_2Br$.

24. The method of claim 21, wherein the perfluoroether is $(BrCF_2OCF_2)_2$.

25. The method of claim 1, wherein the liquid is a hydrofluorocarbon selected from the group consisting of fluorocarbon-hydrocarbon diblocks, fluorocarbon-hydrocarbon ethers, and hydrochlorofluorocarbons.

26. The method of claim 1, wherein the liquid is a mixture of fluorocarbons and highly fluorinated compounds.

27. The method of claim 1, wherein the liquid is a hydrofluoroalkane.

28. The method of claim 1, wherein the liquid is a hydrochlorofluoroalkane.

29. The method of claim 27, wherein the hydrofluoroalkane is selected from the group consisting of CF_3CH_2F, CF_3CHFCH_3, and $CF_3CF_2CF_2H$.

30. The method of claim 1, wherein the liquid mist further comprises at least one fluorinated component.

31. The method of claim 30, wherein the at least one fluorinated component boils below 37 °C.

32. The method of claim 1, wherein the liquid mist further comprises at least one component that boils below 37 °C.

33. The method of claim 32, wherein the at least one component is SF_6.

34. The method of claim 32, wherein the at least one component is He.

35. The method of claim 32, wherein the at least one component is CO_2.

36. The method of claim 30, wherein the at least one fluorinated component is a light fluorocarbon or a hydrofluorocarbon.

37. The method of claim 30, wherein the at least one fluorinated component is a hydrofluoroalkane with a boiling point below 37 °C.

38. The method of claim 30, wherein the at least one fluorinated component is perfluoropentane.

39. The method of claim 30, wherein the at least one fluorinated component is selected from the group consisting of perfluorobutane, perfluorocyclobutane, perfluoropropane, C_3F_7Br, and perfluorotetrahydropyrane.

40. The method of claim 30, wherein the at least one fluorinated component is a light fluorinated ether with a boiling point below 37°C.

41. The method of claim 40, wherein the light fluorinated ether is selected from the group consisting of $C_3F_7OC_2F_5$ and $(C_2F_5)_2O$.

42. The method of claim 1, wherein the liquid has a boiling point of 38 – 80 °C.

43. The method of claim 1, wherein the liquid has a boiling point of 40 – 75 °C.

44. The method of claim 1, wherein the liquid has a boiling point of 38 – 75 °C.

45. The method of claim 1, wherein the liquid has a boiling point of 50 – 70 °C.

46. The method of claim 1, wherein the liquid has a boiling point of 38– 70 °C.

47. The method of claim 1, wherein the liquid is perfluorocyclohexane.

48. The method of claim 20, wherein the perfluoroether is selected from the group consisting of $(C_3F_7)_2O$, $CF_3(OCF_2)_3OCF_3$, $(CF_3OCF_2CF_2)_2O$ and $(CF_2CF_2CF_2CF(C_4F_9)O)$, (iso-$C_3F_7)_2O$, and $C_4F_9OC_2F_5$.

49. The method of claim 20, wherein the perfluoroether is $(C_3F_7)_2O$.

50. The method of claim 20, wherein the perfluoroether is $(CF_3OCF_2CF_2)_2O$.

51. The method of claim 20, wherein the perfluoroether is $CF_3(OCF_2)_3OCF_3$.

52. The method of claim 1, wherein the liquid is selected from the group consisting of perfluoro(n-butyl)tetrahydrofurane, perfluoro-2-(n-butyl)tetrahydrofurane, and perfluoro-3-(n-butyl)tetrahydrofurane.

53. The method of claim 1, wherein the liquid is a hydrofluoroether.

54. The method of claim 53, wherein the hydrofluoroether is selected from the group consisting of $C_4F_9OCH_3$ and $C_4F_9OC_2H_5$.

55. The method of claim 1, wherein the liquid is the hydrofluoroether $C_4F_9OCH_3$.

56. The method of claim 1, wherein the liquid is the hydrofluoroether $C_4F_9OC_2H_5$.

57. The method of claim 32, wherein the hydrochlorofluoroalkane is selected from the group consisting of CH_2ClCF_2Cl and $CHCl_2CHF_2$.

58. The method of claim 1, wherein the mist droplets range in size from 0.1 – 100 microns.

59. The method of claim 1, wherein the mist droplets range in size from 1 – 5 microns.

60. The method of claim 1, wherein the mist droplets range in size from 2 – 4 microns.

61. The method of claim 1, wherein the volume of liquid administered ranges from 0.1 to 20 liters.

62. The method of claim 1, wherein the volume of liquid administered ranges from 2 to 6 liters.

63. The method of claim 1, wherein administration of the liquid is continued until the systemic temperature is reduced to at least 34 °C.

64. A composition for transpulmonary cooling, comprising:

a nebulized liquid in the form of a mist, the liquid having a boiling point of 38 – 300 °C.

65. The composition of claim 64, wherein the liquid has a boiling point range of 38 - 150 °C.

66. The composition of claim 64, wherein the mist droplets range in size from 0.1 - 100 microns.

67. The composition of claim 64, wherein the liquid or liquid mist is cooled to below body temperature before delivery.

68. The composition of claim 64, wherein the liquid or liquid mist is cooled to 10 °C or less before delivery.

69. The composition of claim 64, wherein the liquid is a highly fluorinated compound.

70. The composition of claim 69, wherein the highly fluorinated compound comprises a branched compound.

71. The composition of claim 69, wherein the highly fluorinated compound comprises a cyclic compound.

72. The composition of claim 69, wherein the highly fluorinated compound comprises a saturated compound.

73. The composition of claim 69, wherein the highly fluorinated compound comprises an unsaturated compound.

74. The composition of claim 73, wherein the highly fluorinated compound comprises at least one heteroatom.

75. The composition of claim 73, wherein the highly fluorinated compound comprises at least one hydrogen.

76. The composition of claim 73, wherein the highly fluorinated compound comprises at least one halogen.

77. The composition of claim 64, wherein the liquid is a fluorocarbon.

78. The composition of claim 64, wherein the liquid is a mixture of highly fluorinated compounds or fluorocarbons.

79. The composition of claim 64, wherein the liquid has a boiling point of 38 – 150 °C.

80. The composition of claim 64, wherein the liquid has a boiling point of 38 – 80 °C.

81. The composition of claim 64, wherein the liquid has a boiling point of 38 – 75 °C.

82. The composition of claim 64, wherein the liquid has a boiling point of 40 – 75 °C.

83. The composition of claim 64, wherein the liquid has a boiling point of 38 – 70 °C.

84. The composition of claim 64, wherein the liquid has a boiling point of 50 – 70 °C.

85. The composition of claim 64, wherein the liquid is perfluorohexane.

85. The composition of claim 64, wherein the liquid is perfluorocyclohexane.

86. The composition of claim 64, wherein the liquid is a perfluoroether.

87. The composition of claim 86, wherein the perfluoroether is selected from the group consisting of. $(C_3F_7)_2O$, $CF_3(OCF_2)_3OCF_3$, $(CF_3OCF_2CF_2)_2O$ and $(CF_2CF_2CF_2CF(C_4F_9)O)$, (iso-$C_3F_7)_2O$, and $C_4F_9OC_2F_5$.

88. The composition of claim 86, wherein the perfluoroether is C_3F_7-O-C_3F_7.

89. The composition of claim 64, wherein the liquid is perfluorodiglyme.

90. The composition of claim 64, wherein the liquid is $CF_3(OCF_2)_3OCF_3$.

91. The composition of claim 64, wherein the liquid is $C_4F_9OCH_3$.

92. The composition of claim 64, wherein the liquid is $C_4F_9OC_2H_5$.

93. The composition of claim 64, wherein the liquid is selected from the group consisting of perfluoro(n-butyl)tetrahydrofurane, perfluoro-2-(n-butyl)tetrahydrofurane, and perfluoro-3-(n-butyl)tetrahydrofurane.

94. The composition of claim 64, wherein the liquid is a hydrofluoroether.

95. The composition of claim 94, wherein the hydrofluoroether is selected from the group consisting of $C_4F_9OCH_3$ and $C_4F_9OC_2H_5$.

96. The composition of claim 94, wherein the hydrofluoroether is $C_4F_9OCH_3$.

97. The composition of claim 94, wherein the hydrofluoroether is $C_4F_9OC_2H_5$.

98. The composition of claim 64, wherein the liquid is a hydrochlorofluoroalkane.

99. The composition of claim 64, wherein the liquid further comprises a hydrochlorofluoroalkane selected from the group consisting of CH_2ClCF_2Cl and $CHCl_2CHF_2$.

100. The composition of claim 64, wherein the mist droplets range in size from 0.1 – 100 microns.

101. The composition of claim 64, wherein the mist droplets range in size from 1 – 5 microns.

102. The composition of claim 64, wherein the mist droplets range in size from 2 - 4 microns.

103. The composition of claim 102, wherein the liquid further comprises at least one component that boils below 37 °C.

104. The composition of claim 103, wherein the at least one component is SF_6.

105. The composition of claim 103, wherein the at least one component is He.

106. The composition of claim 103, wherein the at least one component is CO_2.

107. The composition of claim 103, wherein the at least one component is fluorinated.

108. The composition of claim 107, wherein the at least one component is a hydrofluoroalkane.

109. The composition of claim 107, wherein the at least one fluorinated component is perfluoropentane.

110. The composition of claim 107, wherein the at least one fluorinated component is selected from the group consisting of perfluorobutane, perfluorocyclobutane, perfluoropropane, perfluorotetrahydropyrane.

111. The composition of claim 107, wherein the at least one fluorinated component is selected from the group consisting of $C_3F_7OC_3F_5$ and $(C_2F_5)_2O$.

112. A medical device for transpulmonary cooling, comprising:

an inhaler device; and

a nebulized liquid in the form of a mist the liquid having a boiling point of 38 – 300 °C.

113. The medical device of claim 112, wherein the liquid or liquid mist is cooled to below body temperature before delivery.

114. The medical device of claim 112, wherein the liquid or liquid mist is cooled to 10 °C or less before delivery.

115. The medical device of claim 112, wherein the liquid is a highly fluorinated compound.

116. The medical device of claim 115, wherein the highly fluorinated compound comprises a branched compound.

117. The medical device of claim 115, wherein the highly fluorinated compound comprises a cyclic compound.

118. The medical device of claim 115, wherein the highly fluorinated compound comprises a saturated compound.

119. The medical device of claim 115, wherein the highly fluorinated compound comprises an unsaturated compound.

120. The medical device of claim 119, wherein the highly fluorinated compound comprises at least one heteroatom.

121. The medical device of claim 119, wherein the highly fluorinated compound comprises at least one hydrogen.

122. The medical device of claim 119, wherein the highly fluorinated compound comprises at least one halogen.

123. The medical device of claim 112, wherein the liquid is a fluorocarbon.

124. The medical device of claim 112, wherein the liquid is a mixture of fluorocarbons.

125. The medical device of claim 112, wherein the liquid has a boiling point of 38 – 150 °C.

126. The medical device of claim 112, wherein the liquid has a boiling point of 38 – 80 °C.

127. The medical device of claim 112, wherein the liquid has a boiling point of 40 – 75 °C.

128. The medical device of claim 112, wherein the liquid has a boiling point of 38 – 70 °C.

129. The medical device of claim 112, wherein the liquid has a boiling point of 50 – 70 °C.

130. The medical device of claim 112, wherein the liquid is perfluorohexane.

131. The medical device of claim 112, wherein the liquid is perfluorocyclohexane.

132. The medical device of claim 112, wherein the liquid is a perfluoroether.

133. The medical device of claim 132, wherein the perfluoroether is selected from the group consisting of. $(C_3F_7)_2O$, $CF_3(OCF_2)_3OCF_3$, $(CF_3OCF_2CF_2)_2O$ and $(CF_2CF_2CF_2CF(C_4F_9)O)$, (iso-$C_3F_7)_2O$,, and $C_4F_9OC_2F_5$.

134. The medical device of claim 112, wherein the liquid is C_3F_7-O-C_3F_7.

135. The medical device of claim 112, wherein the liquid is perfluorodiglyme ($(CF_3OCF_2CF_2)_2O$).

136. The medical device of claim 112, wherein the liquid is $CF_3(OCF_2)_3OCF_3$.

137. The medical device of claim 112, wherein the liquid is $C_4F_9OCH_3$.

138. The medical device of claim 112, wherein the liquid is $C_4F_9OC_2H_5$.

139. The medical device of claim 112, wherein the liquid is selected from the group consisting of perfluoro(n-butyl)tetrahydrofurane, perfluoro-2-(n-butyl)tetrahydrofurane, and perfluoro-3-(n-butyl)tetrahydrofurane.

140. The medical device of claim 112, wherein the liquid is a hydrofluoroether.

141. The medical device of claim 140, wherein the hydrofluoroether is selected from the group consisting of $C_4F_9OCH_3$ and $C_4F_9OC_2H_5$.

142. The medical device of claim 140, wherein the hydrofluoroether is $C_4F_9OCH_3$.

143. The medical device of claim 140, wherein the hydrofluoroether is $C_4F_9OC_2H_5$.

144. The medical device of claim 112, wherein the liquid is a hydrochlorofluoroalkane.

145. The medical device of claim 112, wherein the liquid further comprises a hydrochlorofluoroalkane selected from the group consisting of CH_2ClCF_2Cl and $CHCl_2CHF_2$.

146. The medical device of claim 112, wherein the mist droplets range in size from about 0.1 – 100 microns.

147. The medical device of claim 112, wherein the mist droplets range in size from 1 – 5 microns.

148. The method of claim 6, further comprising the step of recovering the at least one highly fluorinated compound.

149. The method of claim 148, further comprising the step of recirculating the at least one highly fluorinated compound.

150. A method for transpulmonary cooling, comprising the steps of:

providing a liquid fluorocarbon;

nebulizing the liquid to form a mist;

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling;

recovering the fluorocarbon from an expired gas; and

recirculating the recovered fluorocarbon to the patient.

151. The method of claim 150, wherein the step of recirculating the recovered fluorocarbon to the patient comprises the steps of:

nebulizing the recovered fluorocarbon to form a mist; and

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling.

152. A method for transpulmonary cooling, comprising the steps of:

providing a liquid having a boiling point of 38 – 300 °C;

nebulizing the liquid to form a mist; and

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling.

153. The method of claim 152, wherein the mist delivered to the airway of a patient further comprises saline mist.

154. The method of claim 152, wherein the mist delivered to the airway of a patient further comprises a pulmonary vasodilator.

155. The method of claim 154, wherein the pulmonary vasodilator is selected from the group consisting of NO, NO/O2, NO/air, and NO/SF6.

156. The method of claim 152, wherein the mist delivered to the airway of a patient further comprises an agent that maintains normal cerebral vascular tone.

157. The method of claim 156, wherein the agent is carbon dioxide.

158. The method of claim 152, further comprising the steps of:

terminating the delivery of the mist to the airway of a patient after a period of more than 3 seconds of delivering the mist to the airway of a patient;

delivering a dry gas to the airway of a patient so that the patient inhales the dry gas for a period of more than 3 seconds;

terminating the delivery of the dry gas to the airway of a patient;

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling.

159. The method of claim 158, wherein the dry gas is selected from the group consisting of cold dry air, cold dry helium-oxygen mixture, and cold dry sulfur hexafluoride.

160. A composition for transpulmonary cooling, comprising:

a nebulized liquid in the form of a mist, the liquid having a boiling point of 38 – 300 °C.

161. The composition of claim 160, wherein the mist further comprises saline mist.

162. The composition of claim 160, wherein the mist further comprises a pulmonary vasodilator.

163. The composition of claim 162, wherein the pulmonary vasodilator is selected from the group consisting of NO, NO/O2, NO/air, and NO/SF6.

164. The composition of claim 160, wherein the mist further comprises an agent that maintains normal cerebral vascular tone.

165. The composition of claim 164, wherein the agent is carbon dioxide.

166. A medical device for transpulmonary cooling, comprising:

an inhaler device; and

a nebulized liquid in the form of a mist the liquid having a boiling point of 38 – 300 °C.

167. The medical device of claim 166, wherein the liquid or liquid mist further comprises saline mist.

168. The medical device of claim 166, wherein the liquid or liquid mist further comprises a pulmonary vasodilator.

169. The medical device of claim 168, wherein the pulmonary vasodilator is selected from the group consisting of NO, NO/O2, NO/air, and NO/SF6.

170. The medical device of claim 166, wherein the liquid or liquid mist further comprises an agent that maintains normal cerebral vascular tone.

171. The medical device of claim 170, wherein the agent is carbon dioxide.

172. A method for transpulmonary cooling, comprising the steps of:

providing a liquid fluorocarbon;

nebulizing the liquid to form a mist;

delivering the mist to the airway of a patient so that the patient inhales the mist to cause systemic cooling;

recovering the fluorocarbon from an expired gas; and

recirculating the recovered fluorocarbon to the patient.

173. The method of claim 172, wherein the mist further comprises saline mist.

174. The method of claim 172, wherein the mist further comprises a pulmonary vasodilator.

175. The method of claim 174, wherein the pulmonary vasodilator is selected from the group consisting of NO, NO/O2, NO/air, and NO/SF6.

176. The method of claim 172, wherein the mist further comprises an agent that maintains normal cerebral vascular tone.

177. The method of claim 176, wherein the agent is carbon dioxide.

178. A method for transpulmonary cooling, comprising the steps of:

providing a substance containing NO in an amount of about 2 to about 80 parts per million, wherein the substance is selected from the group consisting of cold air, a cold gas, a cold liquid, cold PFC, and cold nebulized PFC; and

delivering the substance to the airway of a patient so that the patient inhales the substance to cause systemic cooling.