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(54) Title: XENON-BASED GASEOUS ANAESTHETIC TO BE ADMINISTERED VIA A HEART LUNG MACHINE

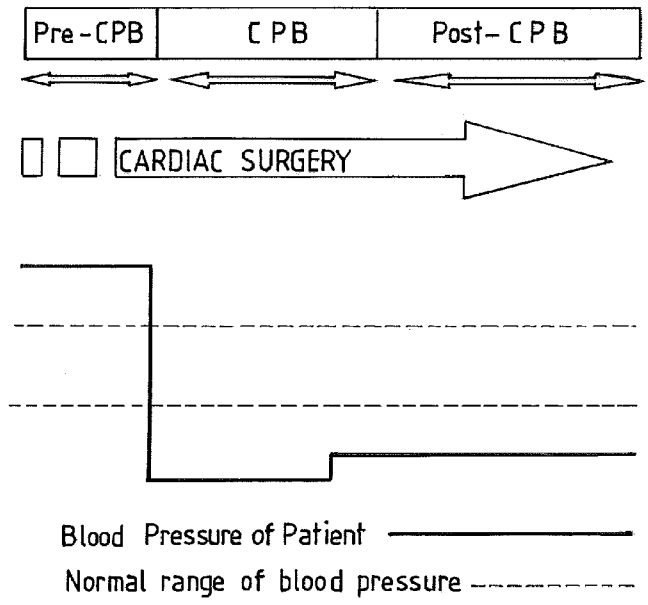

FIG.3

(57) Abstract: An apparatus and a method for maintaining or for providing an anesthesia to a patient undergoing a CPB procedure, comprising the steps of extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure of xenon, circulating the extracted blood through a heart-lung machine comprising at least a membrane having a liquid side and a gas side, contacting a xenon-containing gas with the gas side of the membrane of the heart-lung machine, while contacting, at the same time, the patient's blood circulating through the heart-lung machine with the liquid side of the membrane, applying or maintaining a second partial pressure of xenon on the gas side of the membrane, and re-introducing into the patient's body, the xenon-containing blood coming from the heart-lung machine and having been in contact with the membrane.

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Xenon-based Gaseous Anaesthetic To Be Administered Via a Heart Lung Machine

Field of the Invention

The present invention relates to a method and an apparatus for providing anaesthesia to a patient undergoing cardiopulmonary bypass (CPB).

Background

Some surgical procedures require the temporary cessation of the normal activity of the heart and/or lungs of a patient, e.g., lung surgery, aortic repair surgery, cardiac surgery. To maintain the perfusion of the organs, oxygenation of the blood and the removal of carbon dioxide from the blood are achieved using extracorporeal oxygenators, such as bubble oxygenators, hollow fibre membranes, membrane plates or the like, and a blood pumping system. Devices combining an oxygenator and pumping system are known as cardiopulmonary bypass (CPB) systems or by the more common name, heart-lung machines. Such devices are described for example in documents U.S. Patent No. 5,858,238 and U.S. Patent No. 6,398,751.

CPB systems are also used in the case of severe lung failure, such as ECMO or extracorporeal membrane oxygenation, with or without insufficiency of the cardiac system. Patients undergoing cardiopulmonary bypass should be anaesthetized in order to render them insensitive to pain during the medical intervention. Currently, anaesthesia is administered before, during and after the CPB phase by intravenous administration of one or more pain-reducing substances in combination with sleep inducing hypnotic agents. This can also be achieved by administering to the patients volatile anaesthetics by inhalation, as in classical anaesthesia.

However, the agents or substances used during CPB to achieve anaesthesia can have severe side effects, impair organ function, cause intra- and postoperative complications and increase mortality. The most severe damage observed with the use of such agents or substances involves impairment of the pumping function of the heart and a decrease in blood pressure, which can subsequently lead to organ hypo-perfusion. In turn, organ hypo-perfusion can lead to the general dysfunction of a variety of organs, which may cause irreversible damage to the body.

Further, intravenous anaesthetic agents, commonly called IV agents, are normally metabolized in the liver. However, in patients with certain diseases, limited capacity of the rate of metabolism in the liver results in various problems associated with the administering of such IV agents, including an unpredictable prolonging of the IV agent's effects in the patients, in adverse side effects for the patient and, in some cases, in fatal over-dosages. In

an attempt to minimize or avoid these problems, it has been proposed to administer volatile anaesthetic agents during CPB, such as sevoflurane, desflurane or similar agents. However, volatile anaesthetic agents are not ideal since they also have drawbacks, in particular, nausea, a decrease in heart function and a reduction of blood pressure. Furthermore, volatile anaesthetics can also impair liver function by decreasing the organ's oxygen supply, whereas their specific metabolism would require an increase of the oxygen supply to the liver to support the liver's metabolic function. The resulting energetic imbalance can lead to irreversible destruction of liver cells. The damage can be even more severe if toxic metabolites are produced.

During the time that a patient is attached to the CPB machine, oxygenation of the blood and the pumping function of the heart are achieved using a relatively primitive system consisting of several roller pumps that pump and circulate the blood through an oxygenator membrane having a liquid (or blood) side and a gas side, which on the gas side, has an oxygen-containing gas, such as a nitrogen/oxygen gas mixture, passively streamed into contact with the gas side of the oxygenator membrane. Diffusion of oxygen into the blood and CO_2 out of the blood, i.e. versus the CO_2 remaining on the gas side of the membrane, occurs thanks to the partial pressure differences of these gases on both sides of the membrane.

There exist some predictable technical risks in the administration of volatiles anaesthetic agents during CPB due to the physical properties of these agents. Indeed, the potency of a volatile anaesthetic agent and the incidence of adverse effects is a function of the volume content of the substance in the blood and/or the organ tissues. The gaseous volume (at constant atmospheric pressure) depends on the vapour pressure of the gas, which is influenced in a non-linear way by its temperature.

A primary risk that results from administering volatile anaesthetic agents during CPB is rapid change of the blood temperature that usually happens during a CPB procedure. Indeed, the blood temperature during CPB ranges from about 16° C (corresponding to the deep hypothermia period during which the temporary total arrest of cardiac function occurs) to about 40°C (corresponding to the re-warming/re-perfusion period that follows the deep hypothermia period). Within this temperature range, the vapour pressures of volatile agents differs from between about 500% to about 700%, leading therefore, from time to time, as compared to the normal blood temperature of 37.6 °C, to severe over-dosages, possible toxicity and/or adverse side effects, or to the contrary, under-dosages, and in certain cases possible intra-operative awareness of the patient and recall.

This is illustrated by the curve of Figure 1, which shows the temperature dependant known vapour pressures of one chlorofluorocarbon (CFC), i.e. bromochlorodifluoromethane, which is from a comparative class of substances but is not

used as an anaesthetic agent. As can be clearly observed from the curve, the vapour pressure of the CFC compound at 16° C equals about 800 mbar, whereas at 40°C the vapour pressure equals about 5 bar.

Another existing risk results from the properties of the compounds of the volatile agent group that are known to be corrosive and soluble in fat, oil, plastics and rubbers. As a consequence, halogenated fluorocarbons can react with one or more plastic components of the CPB system thereby leading to dysfunction or inoperability of the oxygenation membranes and/or the dissolving of lubricants used in the pumps, and consequently the impairment of the function of the CPB system. The Table below illustrates the degree of compatibility of trichlorofluoromethane with some known plastics.

Table

Material	Compatibility
Kel-F ®	Slight swelling
Teflon ®	Good
Epoxy resins	Good
Phenolic resins	Should be tested
Cellulose acetate	Good
Polystyrene	Incompatible
Polyethylene	May be compatible at room temperature but needs thorough testing first
Nylon ®	May become brittle at high temperature in the presence of water and air
Vinyl resin	Should be tested

Further, undesirable reactions of CFC compounds with plastic components can also lead to the formation of toxic compounds that a patient undergoing the CPB operation should not be exposed to.

In an attempt to overcome some of these problems, it has been proposed to use xenon gas as an anaesthetic agent during CPB operations. See e.g., G. Lockwood et al, *Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: phase I study* ; *Anesthesiology* 2006; 104: pp.458-65.

Indeed, xenon is a good candidate for providing anaesthesia during a CPB operation as it does not react with oil, plastics and rubbers and, furthermore, does not have a vapour pressure that is highly influenced by rapid changes of the blood temperature of the patient. In addition, xenon preserves patient blood pressures within normal ranges not only before and after CPB, but also during the CPB phase, when the blood is circulating through the CPB machine.

Furthermore, xenon is also able to limit the negative side effects of a CPB on the pump function of the heart and on the blood pressure of the patient, and their consequences, such as organ mal perfusion and postoperative dysfunctions. For instance, U.S. Patent Publication No. 2005/238726 discloses methods of controlling neurological deficits in

patients who have undergone cardiopulmonary bypass (CPB), wherein xenon is administered prior to the commencement, during and after the CPB phase and when blood is extracted from the body. According to a preferred embodiment, oxygen/xenon is administered by perfusion using a specialized heart-lung machine into the patient undergoing the CPB procedure along with the removal of carbon dioxide.

It is also known from document European Patent 1318797-A that xenon can be co-administrated with other anaesthetic agents during CPB. Actually, co-administrating xenon is advantageous since doing so requires lower doses of anaesthetic compounds, i.e. volatile and/or injectable anaesthetic agents that have to be co-administered with the anaesthetic agent, especially during the CPB phase, but preferably also before and after the CPB phase.

However, the drawbacks of using xenon as an anaesthetic agent during a CPB operation are that it is costly due to the non negligible consumption of xenon in the heart-lung machine during the CPB procedure and that it also raises safety issues due to the loss of xenon in the waste gases of the heart-lung machine that are normally vented to the atmosphere, i.e. in the operation room or similar area.

Indeed, to ensure the blood/gas exchanges in the heart-lung machine, a membrane system is commonly used. More precisely, a continuous flow of a gas mixture containing xenon and oxygen is contacted with the gas side of the membrane included in such a membrane system (such as a hollow-fibre membrane) whereas the patient's blood is, more or less at the same time, contacted with the other side of the membrane, i.e. the "blood side", thereby resulting in gas exchanges through the membrane between the gas side and the blood side of the membrane.

Oxygen and xenon gases diffuse through the membrane and are subsequently dissolved in the blood, whereas CO_2 is released by the blood (passed from the blood side to the gas side) and recovered on the gas side of the membrane before being recovered and vented to the atmosphere as waste gases. In other words, in a heart-lung machine, the waste gases are not reintroduced into the membrane system but are instead vented and lost in the ambient air, i.e., in the operation room.

Actually, it has been observed in practice that, during the gas exchange that takes place in the membrane system of the heart-lung ventilator, a non-negligible amount of xenon may also diffuse through the membrane, like the CO_2 molecules, and is vented afterwards along with the CO_2 into the atmosphere. This of course leads to the loss of xenon and to an increased consumption of fresh xenon since the lost xenon must be replaced with fresh xenon in order to maintain the desired quantity of xenon dissolved in the blood. In other words, all the vented and lost xenon should be counterbalanced by fresh xenon. Due to the high cost of xenon, this loss and replacement cycle results in an added expense.

Also, if the rate of diffusion of xenon coming from the blood through the membrane is too rapid, i.e. occurs at a higher than intended rate, then the level of anaesthesia administered to the patient may not be sufficient since the amount of xenon dissolved in the patient's blood would be too low, which in turn could lead to possible intra-operative awareness of the patient and recall. This of course is not acceptable.

Recovering, purifying and then recycling the xenon-containing waste gases leaving the membrane system would be possible in theory, but not ideal. In addition, this would be rather difficult to implement in practice as it would increase the complexity of the apparatus and it would further introduce an additional risk for the patient since, in cases where the gas purification is not efficient enough, an amount of impure gas might be reintroduced into the membrane system. This should absolutely be avoided for obvious safety reasons.

Accordingly, in view of the above, the first problem to be solved requires a device and a method for obtaining an efficient anaesthesia for a patient undergoing CPB, wherein xenon gas is used as a anaesthetic agent, alone or in combination with any other anaesthetic substance or compound, which overcomes, at least partially, all or some the above problems and/or drawbacks.

The second problem to be solved requires a device and a method for minimizing losses and consumption of xenon during the anaesthesia of a patient undergoing CPB using xenon as an anaesthetic agent.

The third problem to be solved requires a device and a method for maintaining an efficient anaesthesia of a patient undergoing CPB using xenon as an anaesthetic agent, even during the CPB phase when the blood of the patient is bypassed and travels trough the heart-lung machine.

The fourth problem to be solved requires a device and a method for limiting the diffusion through the membrane of the heart-lung machine used during CPB, of xenon dissolved in the blood of a patient towards the gas side of the membrane.

One or more of these problems are solved by utilizing the method and the apparatus for providing anesthesia according to the various embodiments of the present invention.

Summary of the Invention

One embodiment of the present invention comprises an apparatus for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising :

- a heart-lung machine comprising at least one membrane having a liquid side and a gas side, and further comprising blood circulating means for circulating blood extracted from the patient and containing a first partial pressure (pXe1) of xenon, at least through the heart-lung machine and contacting it with the liquid side of the membrane,

- a source of xenon-containing gas in fluid communication with the gas side of the membrane of the heart-lung machine, and

- partial pressure controlling means for applying or maintaining a second partial pressure (pXe2) of xenon on the gas side of the membrane such that : $pXe2 \geq 0.5 \times pXe1$.

Depending on the embodiment, the apparatus of the present invention can comprise one or several of the following features:

- it further comprises blood extracting means for extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure (pXe1) of xenon, and blood recirculating means for re-introducing into the patient's body, the xenon-containing blood that has been circulated through the heart-lung machine and has been in contact with the membrane. For instance, said blood extracting means and said blood recirculating means can include conducts or similar for convoying the blood from the patient to the heart-lung machine, and vice versa.

- the membrane is a hollow fiber-type membrane with the gas side of the membrane comprising the internal or external part of the fibers.

- the source of xenon-containing gas comprises xenon and oxygen, preferably contains at least vol. 20% of oxygen.

- the membrane is a selective membrane that exhibits a greater coefficient of permeability for O_2 than for xenon, preferably it exhibits a greater coefficient of permeability for CO_2 and O_2 than for xenon.

- the selective membrane is a nanocarbone-type membrane.

Another embodiment of the present invention comprises xenon-containing gas for use in a method for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising the steps described below. Preferably, said xenon-containing gas comprises xenon and oxygen, preferably at least 20 vol. % of oxygen.

According to still another embodiment of the present invention comprises a method for maintaining or providing anesthesia to a patient undergoing an operation in which CPB is used. The steps of the method include: extracting at least a part or portion of the patient's blood from the patient's body, wherein the extracted blood contains a first partial pressure (pXe1) of xenon; circulating the extracted blood through a heart-lung machine comprising at least one membrane having a liquid side and a gas side; contacting a xenon-containing gas with the gas side of the at least one membrane of the heart-lung machine and further contacting the patient's blood that is circulating through the heart-lung machine with the liquid side of the at least one membrane; applying or maintaining a second partial pressure

(pXe2) of xenon on the gas side of the at least one membrane such that : pXe2 ≥ 0.5 x pXe1; and then after the patient's blood has been circulated through the heart-lung machine, re-introducing the xenon-containing blood coming from the heart-lung machine back into the patient's body.

Preferably, in another embodiment, xenon is also administered to the patient by inhalation of an effective amount of gaseous xenon (in the form of a xenon-containing gas) prior to the commencement of the CPB procedure, e.g., when the anesthesia is induced in the patient and the blood has not yet been extracted from the patient's body.

The method of the present invention can include one or several of the following features :

- it comprises xenon and oxygen, preferably it comprises xenon and at least 20 vol. % of oxygen.

- pXe2 ≥ 0.8 x pXe1, preferably pXe2 ≥ 0.9 x pXe1.

- the second partial pressure of xenon (pXe2) applied or maintained on the gas side of the membrane is greater than or equal to (pXe2 ≥pXe1) the first partial pressure of xenon (pXe1) in the blood on the liquid side of the membrane.

- the first partial pressure of xenon (pXe1) in the blood is at least 350 mm Hg (= 465 mbar) measured at a temperature (TXe1) from about between 16°C and 40°C.

- the first partial pressure of xenon (pXe1) in the blood is at least 400 mm Hg (= 533 mbar) measured at a temperature (TXe1) from about between 16°C and 40°C, preferably the first partial pressure of xenon (pXe1) in the blood is at least 480 mm Hg (= 631 mbar).

- in step d), the second partial pressure (pXe2) of xenon applied or maintained on the gas side of the membrane, is obtained by adjusting or controlling the amount of xenon in the xenon-containing gas contacted with the gas side of the membrane.

- the membrane is a hollow fiber-type membrane with the gas side of the membrane comprising the internal or external part of the fibers.

- the xenon-containing gas contacted with the gas side of the membrane comprises xenon and oxygen, preferably contains at least vol. 20% of oxygen.

- the xenon-containing gas is obtained by mixing xenon and oxygen inside the heart-lung machine or the xenon-containing gas is obtained by mixing xenon and oxygen prior to introducing the gas into the heart-lung machine.

- prior to step a), said first partial pressure (pXe1) of xenon in the patient's blood is achieved by administering gaseous xenon to the patient by inhalation, preferably said

gaseous xenon is in the form of a xenon-containing gas comprising xenon and at least oxygen.

- said gaseous xenon is mixed with at least gaseous oxygen, the proportion of gaseous xenon in the gas mixture being from between 5 and 75% in volume.

- during the CPB, the patient is put into hypothermia.

According to another embodiment, the method for maintaining or for providing an anesthesia to a patient undergoing a CPB operation, comprises the steps of :

i) administering to a patient prior to commencement of the CPB operation a first xenon-containing gas, thereby dissolving some xenon in the blood of the patient,

ii) starting the CPB by extracting at least a portion of the patient's blood from the patient's body, said extracted blood containing dissolved xenon and CO_2,

iii) circulating the extracted blood through a heart-lung machine comprising at least a membrane having a liquid side and a gas side, said membrane being a selective membrane that exhibits a greater coefficient of permeability for CO_2 and O_2 than for xenon,

iv) contacting a second xenon-containing gas and an oxygen-containing gas with the gas side of the membrane of the heart-lung machine and contacting the patient's blood circulating through the heart-lung machine, with the liquid side of the membrane, thereby introducing oxygen and xenon into the blood and simultaneously removing CO_2 from the blood by permeation through the selective membrane, oxygen and xenon diffusing through the membrane from the gas side to the liquid side, and CO_2 diffusing through the membrane from the liquid side to the gas side,

v) reintroducing the xenon and oxygen-containing blood coming from the heart-lung machine into the patient's body.

The method according to a second embodiment of the present invention can include one or several of the following features :

- in step i), the amount of gaseous xenon contained in the first xenon-containing gas is from between about 5 and 75 vol. %.

- it further comprises the step of administrating by inhalation a third xenon-containing gas to the patient, after the CPB operation, said third xenon-containing gas containing a volume amount of xenon from between about 5 and 75 vol. %.

- one or more additional anesthetic agents are administrated to the patient during step i).

- the additional anaesthetic agent is at least a volatile compound to be inhaled by the patient, said volatile compound selected from sevoflurane, desflurane, isoflurane, enflurane and mixtures thereof.

- the amount of said volatile compound to be inhaled by the patient is from about between 0.05 vol.% and 15 vol. %.

- the additional anesthetic agent is one or more injectable compounds selected from opiods, hypnotic acting agents, benzodiazepines, barbiturates and mixtures thereof.

- the first, second or third xenon-containing gas further contains from about between 20 and 90 vol. % of oxygen.

- during the CPB operation, the patient is put into hypothermia.

- the selective membrane is a nanocarbone-type membrane.

According to still another embodiment, the method for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising the steps of :

a) extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure (pXe1) of xenon,

b) circulating the extracted blood through a heart-lung machine comprising two separate membranes each having a liquid side and a gas side, one membrane for allowing the diffusion of xenon into blood and the other membrane for allowing the diffusion of oxygen into the blood and CO_2 out of the blood,

c) either contacting a xenon gas with the gas side of the membrane of the heart lung machine that allows for the diffusion of xenon into the blood, while at the same time contacting the patient's blood circulating through the heart-lung machine with the liquid side of the membrane followed by contacting an oxygen gas with the gas side of the membrane of the heart lung machine that allows for the diffusion of oxygen into the blood and CO_2 out of the blood or contacting an oxygen gas with the gas side of the membrane of the heart lung machine that allows for the diffusion of oxygen into the blood and CO_2 out of the blood followed by contacting a xenon gas with the gas side of the membrane of the heart lung machine that allows for the diffusion of xenon into the blood, while at the same time contacting the patient's blood circulating through the heart-lung machine with the liquid side of the membrane,

d) applying or maintaining a second partial pressure (pXe2) of xenon on the gas side of the membrane that allows for the diffusion of xenon into the blood during step c) such that : $pXe2 \geq 0.5 \times pXe1$,

e) re-introducing into the patient's body, the xenon-containing blood that has been circulated through the heart-lung machine and has been in contact with the two membranes.

Brief Description of the Figures

Figure 1 provides a curve showing the vapour pressure of bromochlorodifluoro-methane between -50°C and +150°C.

Figure 2 provides a curve showing the vapour pressure of gaseous xenon (Xe) between -117°C and +20°C.

Figure 3 illustrates the main steps of a CPB procedure.

Detailed Description of the Invention

Xenon is an inert gas that has been used for years as an anaesthetic agent that is inhaled by the patient, i.e. the administering of xenon is normally done via the lungs. Within the framework of the present invention, it is proposed to administer xenon, during the CPB phase, directly into the blood of the patient by means of a heart-lung machine that is equipped with a gas-exchange membrane. Xenon is a commercially available gas that can be purchased from a gas supplier, such as Air Liquide Santé.

The problems discussed in the background can be solved, depending on the embodiment, by either maintaining an adequate xenon partial pressure difference between the gas and blood sides of the one or more membranes utilized, or by using one or more selective membranes, or a combination of both. The present invention provides for a way of maintaining or providing an anesthesia to a patient undergoing a CPB procedure. According to the invention, at least a portion of the patient's blood is extracted from the patient's body, the blood having a first partial pressure (pXe1) of xenon. In one embodiment of the present invention, the first partial pressure of xenon (pXe1) in the blood is at least 350 mm Hg (= 465 mbar) measured at a temperature (TXe1) from about between 16°C and 40°C . In a still further embodiment, the first partial pressure of xenon (pXe1) in the blood is at least 400 mm Hg (= 533 mbar) measured at a temperature (TXe1) from about between 16°C and 40°C, even more preferably at least 480 mm Hg (= 533 mbar) measured at a temperature (TXe1) from about between 16°C and 40°C.

As the blood is extracted from the patient's blood, standard means are used for injecting the patient's blood into and circulating it through the heart-lung machine that includes at least one membrane that has a liquid side and a gas side. As the blood is circulated through the machine, it is allowed to come in contact with the liquid side of the one or more such membranes. A xenon-containing gas is contacted with the gas side of the at least one membrane of the heart-lung machine at the same time that the patient's blood that is circulating through the heart-lung machine is contacted with the liquid side of the at

least one membrane. In this step, the second partial pressure (pXe2) of xenon applied or maintained on the gas side of the at least one membrane is obtained by adjusting or controlling the amount of xenon in the gas mixture (xenon-containing gas) contacted with the gas side of the at least one membrane. Further, a second partial pressure of xenon (pXe2) is applied and/or maintained, using partial pressure controlling means, on the gas side of the at least one membrane such that: $pXe2 \geq 0.5 \times pXe1$ (the second partial pressure of xenon is greater than or equal to 0.5 times the first partial pressure of xenon), preferably $pXe2 \geq 0.8 \times pXe1$, even more preferably $pXe2 \geq 0.9 \times pXe1$. Partial pressure controlling means are or comprise any device or system that is able to control or adjust the partial pressure of xenon on the gas side of the membrane, including gas lines, valves, sensors... Such devices or systems are well known in the art.

In a still further embodiment of the present invention, the second partial pressure of xenon (pXe2) applied or maintained on the gas side of the at least one membrane is greater than or equal ($pXe2 \geq pXe1$), the first partial pressure of xenon (pXe1) in the blood on the liquid side of the at least one membrane. As a result of the simultaneous contact on both sides of the one or more membranes, carbon dioxide from the patient's blood is removed and xenon (as well as any other gas that is included with xenon such as oxygen) is transferred into the patient's blood thereby allowing for a steady level (amount) of xenon to be maintained in the blood of the patient undergoing CPB ; this treated blood is also referred to as xenon-containing blood. Once the patient's blood has been circulated through the heart-lung machine and brought into contact with the at least one membrane of the heart-lung machine, the patient's xenon-containing blood (blood which has had the xenon content adjusted basis the partial pressure of xenon) is reintroduced into the patient's body.

According to the present invention, a third xenon-containing gas may also be administered by inhalation to the patient after the CPB operation. When the third xenon-containing gas is administered, this gas is preferably a xenon-containing gas having a volume amount of xenon from between 5 and 75 volume %.

In an even further embodiment of the present invention, the first partial pressure of xenon is achieved by administering xenon-containing gas to the patient via inhalation, for example using a respiratory mask or an intubation probe, and this level is maintained either utilizing the partial pressure embodiment disclosed below or the selective membrane embodiment disclosed below. When xenon is administered in combination with one or more other gases, such as oxygen, the xenon and other gas(es) can be administered in a variety of manners, preferably by inhalation of a mixture of all of the gases at once. In all embodiments of the present invention, using xenon in lieu of CFC compounds makes it possible to avoid the problems and risks linked to rapid changes of blood temperature of the patient that typically happen during a CPB procedure.

Indeed, as illustrated in Figure 2, the vapour pressure of gaseous xenon equals about 50 bar at 16°C and about 80 bar at 40°C. As a consequence, with xenon the increase of gaseous volumes during CPB is a maximum of 10% of the increase of gaseous volumes obtained with volatile anaesthetics, especially CFC compounds as above explained.

Another advantage of using xenon over intravenous or volatile substances is that xenon preserves patient blood pressures. Indeed, using xenon for anaesthesia, during a CPB procedure, although being known to have less side effects on cardiac pumping function, cerebral vascular function (i.e. preservation of autonomous blood pressure regulation of the brain (cerebral autoregulation)) was never taken into account. The introduction of closed systems using xenon during CPB procedures makes possible the use of xenon during the CPB phases, as shown on Figure 3, i.e. during the pre-CPB phase, the post-CPB phase and also during the CPB phase itself.

The different embodiments of the present invention are based on the use of xenon during cardiac surgery, ECMO or similar procedures, especially during the CPB phase, in anaesthetic concentrations (volume %) from about 5% to about 75%, depending on the age, gender and intra operative body temperature of the patient and on the amount and types of co-administered drugs.

Further, using xenon allows for a decrease in the quantity of required additional drugs to be co-administered. This in turn reduces the adverse effects of those agents while at the same time preserving blood pressures, cerebral auto-regulation of perfusion pressure and cardiac output capabilities. These are favourable properties that prevent primary damage mechanisms which could in a second step lead to more pronounced organ damage or even death.

Furthermore, at least an additional anesthetic agent can be administrated to the patient. Said additional anesthetic agent can be at least a volatile compound to be inhaled by the patient chosen among sevoflurane, desflurane, isoflurane and enflurane. The amount of said volatile compound to be inhaled by the patient typically constitutes from between 0.05 vol.% and 15 vol. %. However, the additional anaesthetic agent can also be at least an injectable compound chosen among opiods or syntethic opioids, hypnotic acting agents like propofol, benzodiazepines, such as midazolame, flunitrazepame or diazepame, barbiturates, like thiopentone or pentobarbital, and any other hypnotic acting agents. The amount of said injectable compound utilized is between the lowest efficient amount and the maximum dosage before over dosage, i.e. the individual limit to its over-dosage. The most suitable amount should be determinate by the physician depending on the parameters of the patient to be treated, such as his age, weight, gender, co-medication(s), concomitant disease, depth of anesthesia as measured using clinical signs, electroencephalographic parameters,

parameters using the patients general oxygen consumption or the patient's brain's oxygen consumption as parameters for the depth of anesthesia.

When the method utilized involves the administering of xenon to the patient via inhalation (pre-CPB) followed by maintaining the level in the blood via partial pressure or selective membranes (during CPB), the patient is first administered an effective amount of xenon in the form of a xenon-containing gas. As used herein, the term "effective amount" means an amount of xenon that is effective in producing the desired effect of anesthesia, for instance an amount which is sufficient in the patient to induce anesthesia.

Preferably, the xenon-containing gas(es) utilized in the present invention (whether the first, second or third xenon-containing gas) contain a preferred volume amount of xenon from between 15 vol. % and 79 vol. %, preferably from between 40% and 79% vol. %, before CPB and a preferred volume amount of xenon from between 15 % and 79 vol. %, preferably from between 20 and 59 vol. %, during and after the CPB phase. In one embodiment, the inhaled xenon-containing gas preferably comprises a mixture of oxygen and xenon with the mixture containing from between 18 % and 90 % of oxygen, preferably between 20 % and 65 % of oxygen, even more preferably from 20 % to 40% of oxygen. In mixtures that are a gaseous mixture of xenon and at least oxygen, the proportion of gaseous xenon in the gas mixture will typically be from between 5 and 75% volume. When the xenon-containing gas comprises a mixture of oxygen and xenon, the xenon-containing gas may be obtained in a variety of manners. For example, the xenon and oxygen may be mixed at the appropriate concentrations prior to the gas being introduced into the heart-lung machine (premixed cylinders). In another embodiment, the xenon and oxygen may be injected as separate steams into the heart-lung machine which will provide a means of mixing the two gases within the machine before they are brought into contact with one or more CPB membranes. In a still further embodiment, the CPB machine will comprise at least two separate membranes, one for allowing the diffusion of xenon into blood and another for allowing the diffusion of oxygen into the blood and CO_2 out of the blood, each membrane located in a separate compartment. In this embodiment, an oxygen stream will be injected into a first compartment that houses the membrane that allows for the diffusion of oxygen into the blood and CO2 out of the blood. This oxygen will be allowed to contact the membrane on one side while the blood from the patient contacts the membrane on the other side of the membrane. Blood treated in this manner will then pass through a separate compartment which contains a membrane which will allow for the diffusion of xenon into the patient's blood. In this compartment, a stream of xenon will be allowed to contact the membrane on one side while the blood from the patient contacts the membrane on the other side of the membrane. In a still further embodiment, the order of the two compartments is reversed.

In many instances, prior to the CPB phase, the patient is pre-medicated with a xenon-containing gas. Therefore, the blood extracted from the patient will already include a certain concentration of xenon and the other gases contained in the xenon-containing gas. During the CPB procedure, blood is extracted from a patient's body utilizing a heart-lung machine. As the blood is extracted from the patient's body, it is pumped through the heart-lung machine and where it is brought into contact with the CPB membrane(s) thereby allowing for the reintroduction of xenon and other gas (i.e., oxygen) and the removal of CO_2 and then at least a part of the patient's blood that contains adjusted levels of xenon and oxygen is reintroduced by the heart-lung machine into the patient's body.

In another preferred embodiment, during the CPB phase, the patient is put in a state of hypothermia. That is to say, the temperature of the body of the patient is decreased to less than 35 °C, typically from between 30°C to 35 °C, and maintained at that temperature or within this temperature range during at least a part of the CPB phase.

First embodiment of the invention = partial pressures

In the present embodiment, a non-selective membrane separates the gaseous side of the CPB system from the liquid side (blood side). Xenon and the other compounds, in particular O_2 and CO_2, normally pass freely through the membrane, from the gas side towards the liquid side, and/or vice versa.

Actually, the partial pressures of a given compound, on each side of the membrane, depend on the specific properties of the compound.

With regard to the present invention, the xenon concentrations on the gas side of the membrane will range from about 10 ppm to about 80 vol. %. It is important to keep a partial pressure of xenon on the gas side of the membrane that is very close or higher than the partial pressure of xenon in the blood, i.e., on the liquid side of the membrane. This is necessary in order to block or limit the diffusion of xenon from the liquid (blood) side of the membrane towards the gas side of the membrane thereby limiting the loss of xenon.

On the liquid side of the membrane, i.e. the blood side, it is required to have and keep a xenon partial pressure that is sufficient to obtain and maintain anaesthesia. A partial pressure of xenon from about 50 to about 80 vol.%, preferably about 60 to about 70 vol.% is preferred, but those of ordinary skill in the art will recognize that the amount can be decreased based on the decrease of the blood temperature. Under normal temperature conditions, i.e. at about 37°C, a partial pressure of xenon of about 70% means about 70% of 1013 mbar or about 70% of 760 mm Hg, i.e. about 500 to 530 mm Hg (i.e. about 710 mbar).

At the same time, oxygen partial pressure in the blood should be kept above low limits, i.e. above about 21 vol. %. Indeed, normal oxygen blood tension is from 21% to 100% of 760 mm Hg, from which should be deduced the partial pressure of the other gas(es) dissolved in the blood, i.e. typically CO_2 since CO_2 molecules replace O_2 molecules

in the blood. As CO_2 has a partial pressure of about 40 mm Hg in the blood entering in the heart-lung machine, at room temperature (i.e. about 25°C), an oxygen tension of 21% corresponds to an oxygen partial pressure of about 110 mm Hg (i.e. 21% x 760 mm Hg – 40 mm Hg).

This shows that oxygen partial pressure does not change when oxygen tension is 21% and when xenon is added to the blood since xenon molecules do not replace O_2 molecules; in that case the partial pressure of xenon is from about 500 to 530 mm Hg.

However, xenon partial pressure will change if oxygen is added to the blood in concentrations higher than 21 %, i.e. if the oxygen partial pressure is increased. For example, for an oxygen partial pressure of 380 mm Hg and a same CO_2 partial pressure of 40 mm Hg in blood, the resulting partial pressure of xenon in the blood will only be 340 mm Hg (i.e. 760 mm Hg – 420 mm Hg) in lieu of about 500 mm. In view of this, it can be easily understood that the partial pressure of xenon in the blood varies when the concentration of oxygen in the blood varies.

Hence, to avoid an excessive consumption of xenon or, in the opposite situation, a too low administration of xenon during the CPB phase or procedure, it is important to precisely control the partial pressure of xenon on the gas side of the membrane during the CPB in order to keep the partial pressure of xenon on the gas side of the membrane as close as possible to the partial pressure of xenon in the blood.

In an alternative embodiment, the partial pressure of xenon on the gas side of the membrane will be kept higher than the partial pressure of xenon found in the blood, i.e. on the liquid side of the membrane.

This can be done, for example, by adjusting the proportion of gaseous xenon (or oxygen) in a xenon/oxygen mixture to be contacted with the gas side of the membrane thereby maintaining an adequate level of anesthesia during the CPB phase and at the same time decreasing the quantity of lost xenon or of fresh xenon that has to be consumed, i.e. added back to the system.

The membrane to be used during the CPB phase in the present invention can be any non-selective membrane which is capable of allowing the passage of xenon into the blood. Such non-selective membranes are preferably hollow fiber-type membranes or flat sheets made of various materials, either porous or non-porous, and include, but are not limited to, membranes made of silicone, bisphenol, sulfone, carbonate, polysulfone, polycarbonate, cellulose (acetate), copolymidine, ethylocellulose, polyamide nylon, polyethersulfone, polyimide, polypyrrolone, polyvinyl acetate or any other suitable material. In a preferred embodiment of the present invention, the membrane is a hollow fiber-type membrane with the gas side of the membrane comprising the internal or external part of the fibers. Such membranes are readily known in the art.

<u>Second embodiment of the invention = selective membrane</u>

In a further embodiment of the present invention, a selective membrane separates the gaseous side of the CPB system from the liquid side or blood side. In principle, selective membranes separate gas mixtures allowing at least one of the compounds in the gas mixture to diffuse more or less freely through the material that constitutes the membrane, whereas one or more of the others compounds in the gas mixture are almost totally, if not completely, retained, i.e. do not diffuse through the membrane. In other words, different gaseous compounds pass through a selective membrane at different rates and time constraints.

In the present case, the selective membrane to be used during CPB should allow a free exchange of O_2 and CO_2 molecules between its gas side and its blood side for O_2, and vice versa for CO_2, but should at the same time, block or at least limit the passage or diffusion of xenon from the blood side to the gas side in order to decrease the loss of xenon in the waste gases that are subsequently vented.

Choosing such a selective membrane for use in the framework of the present invention can be done empirically via routine testing by a physician as the diffusibility of xenon through such membranes is readily known. Using such a selective membrane will indirectly lead to the control of the partial pressure of xenon in the blood thereby minimizing the loss of xenon while at the same time maintaining an adequate level of xenon for ensuring efficient anesthesia during the CPB phase.

For instance, when using a selective membrane with a selectivity quotient of 2 for xenon (with respect to the total amount of gaseous mass transfer through the membrane) ideally only 170 mm Hg of xenon are necessary on the gas side in order to maintain a partial pressure of xenon of 340 mm Hg on the blood side.

Highly selective membranes that can be used in the method according to the present embodiment of the invention are nanocarbone membranes. Such nanocarbone membranes allow a free transfer of oxygen and CO_2, which must be exchanged during the CPB procedure (which is the typical work of the lung) but limit the passage of xenon from the blood side to the gas side.

However, other types of known selective membrane materials can also be used in the present invention, such as e.g. poly-methyl-pentene (PMP) or carbon with engraved filtration capillaries (NC – nanocarbone).

The selective membranes for use in the present invention are preferably hollow fibre-type membranes or flat sheet-type membranes, although other types of membranes are not excluded from the present invention. When the membrane is a hollow fiber-type membrane, it preferably has a gas side of the membrane that comprises the internal or external part of the fibers.

Xenon selective membranes are preferably used during the CPB procedure, like cardiac surgery or ECMO, in which xenon has been administered to the patient already before the start of the CPB procedure by means of a conventional ventilation of the lungs (inhalation utilizing any known means of administering gases).

It should be emphasized that, according to a third embodiment, the use of a selective membrane can be combined with an adjustment of the partial pressure of xenon on the gas side of the membrane as above described in the first embodiment. Indeed, during a CPB procedure, xenon gas has to be administered into the membrane system, i.e. the oxygenator, to compensate for the loss of xenon due to a permeation of small amounts of xenon through the membrane material. This will occur even in highly selective membrane materials.

CLAIMS

1. Apparatus for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising :

- a heart-lung machine comprising at least one membrane having a liquid side and a gas side, and further comprising blood circulating means for circulating blood extracted from the patient and containing a first partial pressure (pXe1) of xenon, at least through the heart-lung machine and contacting it with the liquid side of the membrane,

- a source of xenon-containing gas in fluid communication with the gas side of the membrane of the heart-lung machine, and

- partial pressure controlling means for applying or maintaining a second partial pressure (pXe2) of xenon on the gas side of the membrane such that : $pXe2 \geq 0.5 \times pXe1$.

2. Apparatus according to Claim 1, characterized in that it further comprises :

- blood extracting means for extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure (pXe1) of xenon, and

- blood recirculating means for re-introducing into the patient's body, the xenon-containing blood that has been circulated through the heart-lung machine and has been in contact with the membrane.

3. Apparatus according to Claim 1 or 2, characterized in that the membrane is a hollow fiber-type membrane with the gas side of the membrane comprising the internal or external part of the fibers.

4. Apparatus according to any one of the previous Claims, characterized in that the source of xenon-containing gas comprises xenon and oxygen, preferably contains at least vol. 20% of oxygen.

5. Apparatus according to any one of the previous Claims, characterized in that the membrane is a selective membrane that exhibits a greater coefficient of permeability for O_2 than for xenon, preferably it exhibits a greater coefficient of permeability for CO_2 and O_2 than for xenon, preferably the selective membrane is a nanocarbone-type membrane.

6. Xenon-containing gas for use in a method for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising the steps of :

a) extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure (pXe1) of xenon,

b) circulating the extracted blood through a heart-lung machine comprising at least one membrane having a liquid side and a gas side,

c) contacting the xenon-containing gas with the gas side of the membrane of the heart-lung machine, while contacting, at the same time, the patient's blood circulating through the heart-lung machine with the liquid side of the membrane,

d) applying or maintaining a second partial pressure (pXe2) of xenon on the gas side of the membrane during step c) such that : $pXe2 \geq 0.5 \times pXe1$,

e) re-introducing into the patient's body, the xenon-containing blood that has been circulated through the heart-lung machine and has been in contact with the membrane.

7. Xenon-containing gas according to Claim 6, characterized in that it comprises xenon and oxygen.

8. Xenon-containing gas according to Claim 6 or 7, characterized in that it comprises xenon and at least 20 vol. % of oxygen.

9. Method for maintaining or providing an anesthesia to a patient undergoing a CPB procedure, comprising the steps of :

a) extracting at least a part of the patient's blood from the patient's body, said blood containing a first partial pressure (pXe1) of xenon,

b) circulating the extracted blood through a heart-lung machine comprising at least one membrane having a liquid side and a gas side,

c) contacting a xenon-containing gas with the gas side of the membrane of the heart-lung machine, while contacting, at the same time, the patient's blood circulating through the heart-lung machine with the liquid side of the membrane,

d) applying or maintaining a second partial pressure (pXe2) of xenon on the gas side of the membrane during step c) such that : $pXe2 \geq 0.5 \times pXe1$,

e) re-introducing into the patient's body, the xenon-containing blood that has been circulated through the heart-lung machine and has been in contact with the membrane.

10. Method of Claim 9, characterized in that : $pXe2 \geq 0.8 \times pXe1$, preferably $pXe2 \geq 0.9 \times pXe1$.

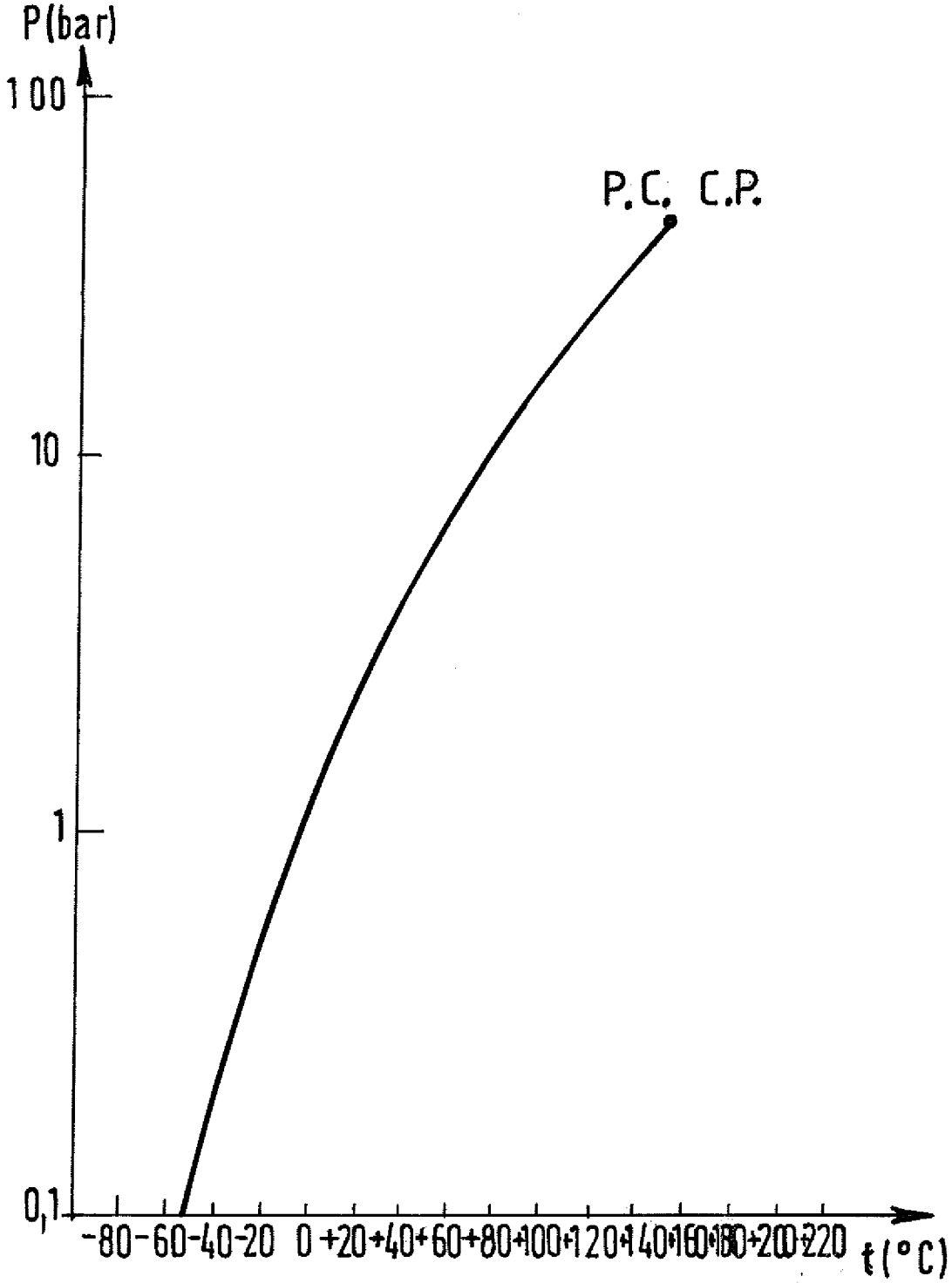
11. Method of Claim 9, characterized in that the second partial pressure of xenon (pXe2) applied or maintained on the gas side of the membrane is greater than or equal to ($pXe2 \geq pXe1$) the first partial pressure of xenon (pXe1) in the blood on the liquid side of the membrane.

12. The method of Claim 9, characterized in that, in step d), the second partial pressure (pXe2) of xenon applied or maintained on the gas side of the membrane, is obtained by adjusting or controlling the amount of xenon in the xenon-containing gas contacted with the gas side of the membrane.

13. The method of Claim 9, characterized in that the membrane is a hollow fiber-type membrane with the gas side of the membrane comprising the internal or external part of the fibers.

14. The method of Claim 9, characterized in that the xenon-containing gas contacted with the gas side of the membrane comprises xenon and oxygen, preferably contains at least vol. 20% of oxygen.

15. The method of Claim 9, characterized in that the xenon-containing gas is obtained by mixing xenon and oxygen inside the heart-lung machine or the xenon-containing gas is obtained by mixing xenon and oxygen prior to introducing the gas into the heart-lung machine.



BROMOCHLORODIFLOROMETHANE

FIG.1

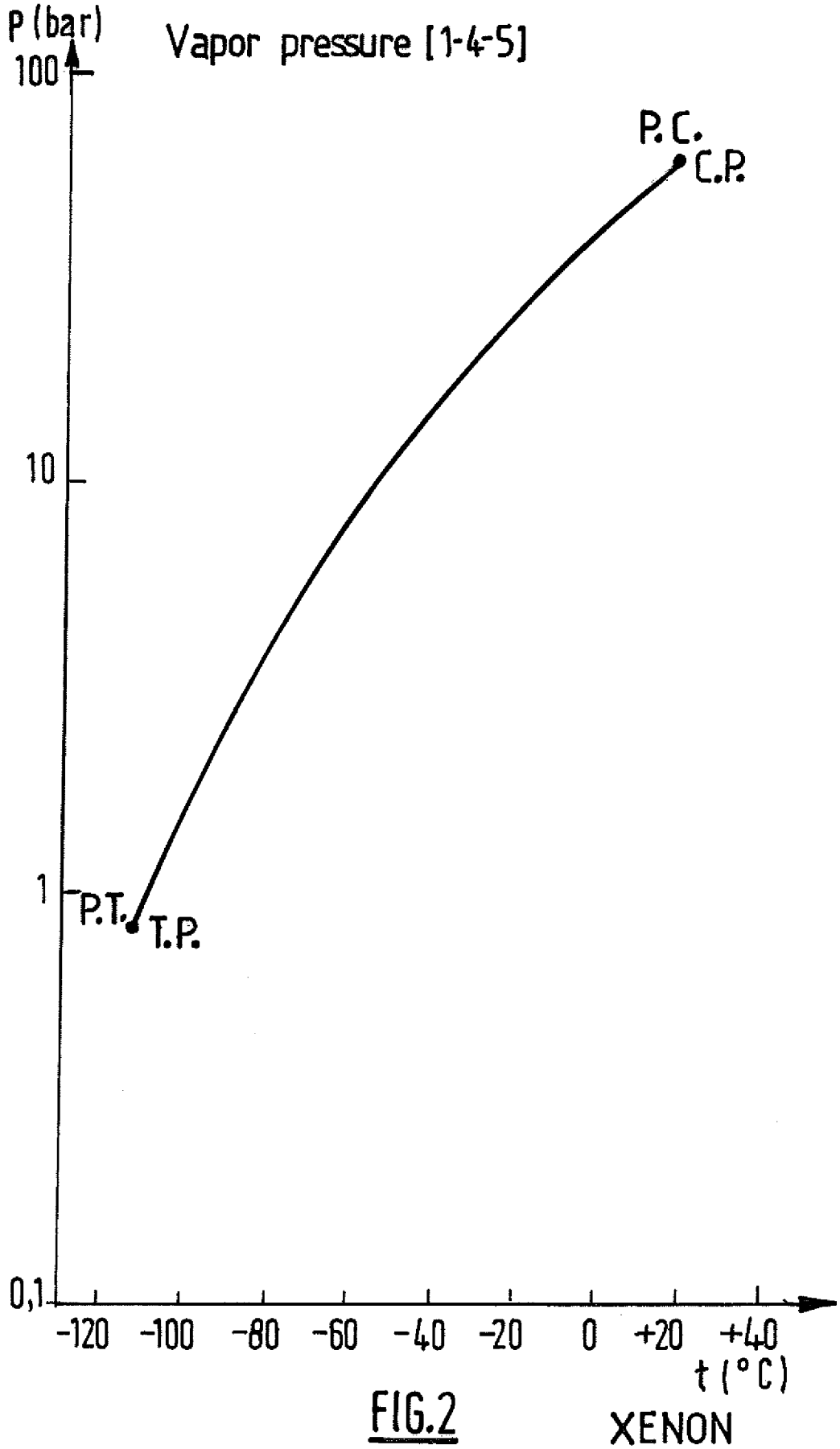

P (bar)
Vapor pressure [1-4-5]
100
10
1
0,1
P.C.
C.P.
P.T.
T.P.
-120
-100
-80
-60
-40
-20
0
+20
+40
t (°C)

FIG.2 XENON

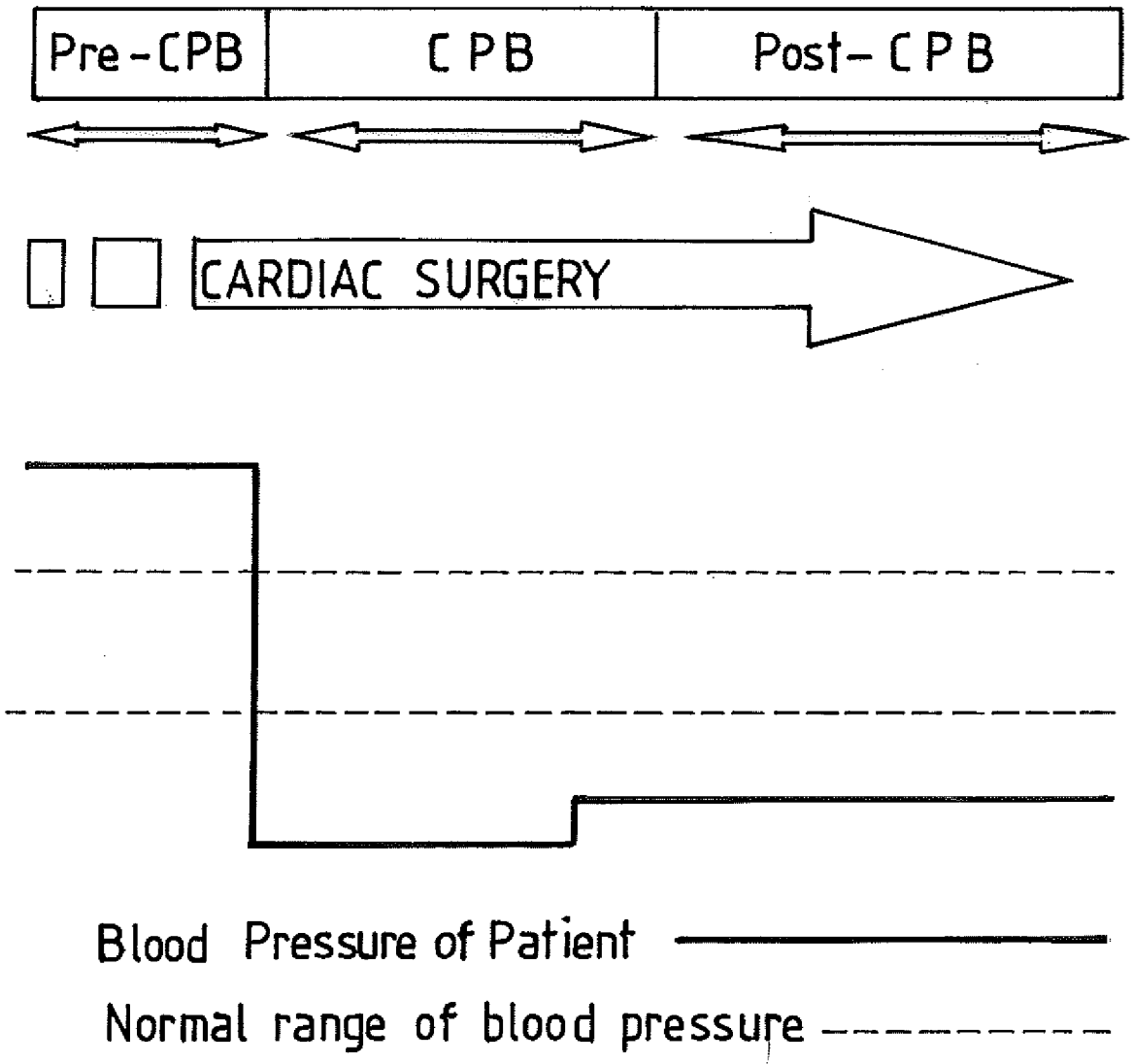

Pre-CPB
CPB
Post-CPB
CARDIAC SURGERY
Blood Pressure of Patient
Normal range of blood pressure

FIG.3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/062528

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M1/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/43792 A1 (ART OF XEN LTD [GB]; DINGLEY JOHN [GB]) 6 June 2002 (2002-06-06) page 3, line 19 - page 6, line 3 page 8, line 9 - page 9, line 4 figures 1-4	1-4
X	WO 2005/092417 A1 (INO THERAPEUTICS GMBH [AT]; MUELLNER RAINER [AT]) 6 October 2005 (2005-10-06) page 4, line 3 - page 5, line 19 page 6, lines 19-22 figure 1	1-4
A	WO 2008/012350 A1 (SCHMIDT KLAUS [DE]) 31 January 2008 (2008-01-31) page 5, lines 4-26	5

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2010	15/02/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bichlmayer, K

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/062528

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/22116 A1 (MESSER GRIESHEIM GMBH [DE]; HORN NICOLA [DE]; NEU PETER [DE]; THOMA KL) 21 March 2002 (2002-03-21) claim 14	6-8
X,P	WO 2008/122654 A2 (FRANKS NICHOLAS PETER [GB]; MAZE MERVYN [GB]; SACRISTAN MARTIN JUAN CA) 16 October 2008 (2008-10-16) page 4, line 15 - page 5, line 31 page 8, lines 8-10 page 14, lines 12-15	6-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/062528

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-15
because they relate to subject matter not required to be searched by this Authority, namely:

Method for treatment of the human or animal body by surgery and therapy (R. 39(1)iv PCT)

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/062528

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