

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 July 2010 (08.07.2010)

PCT

(10) International Publication Number
WO 2010/077201 A1

(51) International Patent Classification:

A01N 1/02 (2006.01) A61K 31/46 (2006.01)
A61K 31/135 (2006.01) A61K 31/573 (2006.01)
A61K 31/137 (2006.01) A61K 38/11 (2006.01)
A61K 31/198 (2006.01)

(21) International Application Number:

PCT/SE2009/000542

(22) International Filing Date:

30 December 2009 (30.12.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0802678-3 30 December 2008 (30.12.2008) SE
61/210,444 19 March 2009 (19.03.2009) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: A COMPOSITION COMPRISING NOR-ADRENALINE AND AMPHETAMINE FOR ADMINISTERING TO A
BRAIN-DEAD, HEART -BEATING POTENTIAL ORGAN DONOR

(57) Abstract: A composition, an infusion solution, a method for treatment, and a kit for intravascular administration for treat-
ment of a brain-dead, heart-beating, respirated, potential organ donor. The composition comprises non-adrenaline and am-
phetamine or an amphetamine-like substance. The composition may in addition comprise adrenaline, hydrocortisone, thyroxin, in-
sulin, triiodotyronine, dopamine, a vasopressor agent, such as desmopressin, and methylprednisolone. The composition may be
dissolved in pure water, Ringer's acetate solution or physiological sodium chloride solution. The composition is infused in such an
amount as to maintain a mean arterial pressure of about 60 mmHg.



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A composition comprising nor-adrenaline and amphetamine for administering to a brain-dead, heart-beating potential organ donor

5 FIELD OF INVENTION

The present invention relates to a method of handling a potential organ donor immediately after brain death and until organs are harvested, and a composition and an infusion solution.

10 BACKGROUND OF THE INVENTION

It is well known that there is a great shortage of donor organs, which are suitable for transplantation.

Hemodynamic instability during and after brain death of a heart-beating donor is often associated with the deterioration of graft viability, leading to organ exclusion.

15 There is a need for a method of treating the potential organ donor after brain death and before harvesting of organs, which decreases the rejection rate of organs that are harvested from such donor.

SUMMARY OF THE INVENTION

20 Accordingly, an object of the present invention is to mitigate, alleviate or eliminate one or more of the above-identified deficiencies and disadvantages singly or in any combination.

According to an aspect of the invention, there is provided a composition for intravascular administration for treatment of a brain-dead, heart-beating, respired potential
25 organ donor, comprising: nor-adrenaline and an amphetamine or an amphetamine-like substance. The amphetamine-like substance may be at least one of the substances included in the group comprising: Tyramine and Ephedrine and Methylphenidate. The composition may further comprise at least one of: adrenaline, hydrocortisone, thyroxine, insulin, triiodothyronine, dopamine, a vasopressor agent, such as desmopressin, and methylprednisolone.

30 In another aspect, there is provided an infusion solution comprising the composition mentioned above and a pharmaceutically acceptable medium, such as pure water, Ringer's acetate solution or physiological sodium chloride solution.

In a further aspect, there is provided a method for treatment of a brain dead, heart-beating, respired potential organ donor, comprising: infusion of the infusion solution
35 mentioned above, in an amount sufficient for maintaining a mean arterial pressure of at least about 60 mmHg.

In a still further aspect, there is provided a kit for intravenous administration for treatment of a brain dead, heart-beating, respirated potential organ donor, comprising an infusion bag comprising an infusion solution as mentioned above; an infusion pump for pumping the infusion solution to a needle inserted into the vascular system of the donor for
5 controlling the amount of infusion solution entered into the donor and tubings for interconnecting the bag, pump and needle. The kit may comprise several sets of infusion bags, infusion pumps and tubings. The kit may further comprise a computer for controlling the pump or pumps, whereby the computer is operated according to a predetermined control strategy.

10 In a yet further aspect, there is provided a method of infusing a solution into the circulation system of a brain dead, heart-beating, respirated potential organ donor, comprising: determining that the donor is brain dead; continuing or initiating respiration for oxygenation of the blood; infusion of an infusion solution as mentioned above; controlling the infusion, for example by means of a computer. The method may comprise: after determination that the
15 donor is brain dead; initially infusing a second infusion solution having a composition as mentioned above, in which the amphetamine or the amphetamine-like substance has been replaced by a NET inhibitor, such as cocaine; and after a predetermined time, terminating infusion of said second infusion solution and infusion of an infusion solution as mentioned above. Alternatively, the method may comprise after determination that the donor is brain
20 dead; initially infusing a bolus of a NET inhibitor, such as a tricyclic antidepressant.

BRIEF DESCRIPTION OF THE DRAWINGS

Further objects, features and advantages of the invention will become apparent from the following detailed description of embodiments of the invention with reference to the
25 drawings, in which:

Fig. 1 is a schematic view of a nerve terminal;

Figs. 2 and 3 are diagrams showing blood pressures during treatment with the compositions comprising a NET inhibitor according to embodiments;

Fig. 4 is a diagram showing blood pressures during treatment with the compositions
30 comprising amphetamine according to embodiments;

Fig. 5 is a schematic diagram of a kit for administration of an infusion solution according to embodiments;

Fig. 6 is a schematic diagram of another kit for administration of infusion solutions according to embodiments.

DETAILED DESCRIPTION OF EMBODIMENTS

Below, several embodiments of the invention will be described. These embodiments are described in illustrating purpose in order to enable a skilled person to carry out the invention and to disclose the best mode. However, such embodiments do not limit the scope of the invention. Moreover, certain combinations of features are shown and discussed. However, other combinations of the different features are possible within the scope of the invention.

Definitions: In the context of the present description and embodiments the following definitions apply: The term "cocaine analogue" is intended to mean an analogue, which acts in the same or a similar way as cocaine in preserving the organs in a brain-dead, heart-beating, respired donor before harvesting of the organs. The term "Pharmaceutically acceptable" means a non-toxic material that does not decrease the effectiveness of the biological activity of the active ingredients. Such pharmaceutically acceptable buffers, carriers or excipients are well-known in the art, see for example Remington's Pharmaceutical Sciences, 18th edition, A.R Gennaro, Ed., Mack Publishing Company (1990) and handbook of Pharmaceutical Excipients, 3rd edition, A. Kibbe, Ed., Pharmaceutical Press (2000). The term "physiologically acceptable solution" means a solution that does not interfere substantially with the fluids in the body.

An object of the below described embodiments is to improve the outcome of organ harvesting and transplantation from a donor, which has been declared brain-dead but still has a beating heart and which is ventilated.

The process of becoming brain dead is a traumatic experience for the body and its organs. Thus, a thorough understanding of the endocrinal, hormonal and metabolic events before, during and after declaration of brain death would be of interest for determining intervention.

Brain death may be initiated by a massive necrosis of brain cells, which may be due to different causes. Such necrosis may result in increased osmotic pressure in the brain, resulting in water absorption via the blood-brain barrier. Since the skull cannot expand, the intracranial pressure rises considerably.

When the intracranial pressure exceeds the systolic blood pressure, the brain is exposed to an ischemic condition, because blood cannot enter the brain. The brain may react by increasing the heart rate and blood flow and by increasing the systemic vascular resistance. In addition, the adrenal gland increases the level of circulating adrenalin (epinephrine) and nor-adrenaline (nor-epinephrine). This is called the Cushing reflex.

The heart rate may increase by several hundred percent, to a maximum heart rate. The blood pressure may increase to above 200 mmHg. This massive reaction is also called the "catecholamine storm" or "sympathetic autonomous storm". The adrenaline and/or nor-adrenaline levels may increase by 70 times, as described in more detail below.

If this increase of systolic blood pressure is insufficient for delivering blood to the brain, the brain will maintain its ischemic state. However, the brain cannot sustain more than about 10 minutes without blood supply.

If the intracranial pressure, for example due to the increased osmotic pressure, rises to more than about 300 mmHg, the brain cannot withstand such high pressures but disintegrates. The end result will be a progressive brain swelling, and herniation of the hippocampal gyri with lateral pressure of the brainstem, with eventual loss of brainstem function and loss of spontaneous respiration. This may result in herniation of the brain stem through the foramen magnum.

Other causes of (brain) death may result in somewhat different processes.

In Sweden, brain death is defined as irreversible loss of function of the entire brain including the brainstem. There are several indicia of brain death, which are of less interest for the present embodiments. However, after brain death, there is no cerebral blood circulation and no spontaneous respiration. The body temperature should be above 33°C and there should be no drug intoxication.

After brain death, the brain, including the brain stem, cannot retain its function, because it is permanently damaged.

During the "catecholamine storm", the levels of adrenaline and nor-adrenaline may rise considerably. During experiments on dogs, an increase in blood concentration of adrenaline from about 0.40 to 75 nmol/l and an increase of nor-adrenaline from about 0.40 to 12 nmol/l were obtained within one to three minutes.

After occurrence of brain death, the hypothalamic-pituitary-adrenal axis is disrupted. However, necrosis is followed by a release of cytokines, especially IL-6, which stimulates the adrenal gland to produce adrenaline and nor-adrenaline. Eventually, the production of these inotropics will be reduced and after some 60 minutes, the levels of adrenaline and nor-adrenaline will be lower than normal. This will result in vasoplegia by loss of the sympathetic vasotonus.

The pituitary gland also produces antidiuretic hormone (ADH), or vasopressin, which acts on the kidneys in order to control the water resorption. ADH has a short half-life-time of about 15 minutes and a shortage of ADH will occur after some 60 minutes (with large individual variations). Depletion of ADH may result in diabetes insipidus, resulting in production of large quantities of urine in the order of several liters per hour. Unless replacement of fluid takes place, diabetes insipidus will result in hypovolemia, a further reduction of blood pressure and eventual loss of circulation, resulting in ischemic damage of all organs.

Moreover, the pituitary gland produces adrenocorticotrophic hormone (ACTH), which stimulates secretion of glucocorticoids, which stimulates the synthesis of adrenaline and nor-adrenaline.

In addition, the pituitary gland produces thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to secrete the hormones thyroxin (T4) and triiodotyronine (T3). Depletion of T4 and T3 may result in a change from aerobic to anaerobic metabolism in for example the heart, which may result in increased lactate and pyruvate levels.

Because the pituitary gland is dependent on the hypothalamus, the operation of the pituitary gland is reduced or ceases, resulting in decreased circulating levels of for example T3, T4, ADH, ACTH, cortisol and insulin. This results in impaired aerobic metabolism, increased anaerobic metabolism, depletion of high-energy phosphates and increased lactate production.

Side effects of high levels of catecholamines are tachycardia, atrial and ventricular arrhythmias as well as conduction abnormalities.

Pulmonary edema may result after high levels of catecholamines, especially adrenaline.

Because of vasoconstriction caused by catecholamines, the organs may loose perfusion.

Hypothalamus controls body temperature, and the failure of the hypothalamus may result in hypothermia.

There are a number of different strategies suggested in the literature for maintaining organs after brain death. The fact that it is possible with prolonged somatic support has been reported for a pregnant woman with brain death. By full ventilatory and nutritional support, vasoactive drugs, maintenance of normothermia, hormone replacement and other supportive measures, the fetus could be born several weeks after brain death of the mother, thereby improving the survival prognosis for the fetus.

A review article by Kenneth E. Wood and John McCartney entitled: "Management of the potential organ donor" published in Transplantation Reviews 21(2007), pages 204-218, and available online at www.sciencedirect.com, summarizes the state of the art in this field.

In Sweden, it is permitted to maintain the donor for 24 hours after brain death until organ harvesting is performed. After harvesting, the organs are examined for viability and stored, normally under hypothermic conditions until transplantation.

Since ADH decreases rapidly, it is necessary to address this issue. Depletion of ADH sooner or later results in diabetes insipidus with high urine volumes leading to hypovolemia. This has been counteracted by infusion of large volumes of colloidal or crystalloid fluid, such as Ringer's solution. Another approach is to add a vasopressor agent, such as arginine vasopressin, desmopressin, DDAVP or Minirin.

The decrease of thyroid hormone level should also be addressed in order not to aggravate metabolism. Thus, addition of T4 and/or T3 may be appropriate.

The reduction in ACTH and cortisol may be addressed by giving methylprednisolone, or a similar agent.

5 In order to maintain proper perfusion of the organs, especially the kidney, it is considered that a mean arterial pressure MAP of at least 60 mmHg should be upheld, see for example the above-mentioned review article. This may be done by adding catecholamines, such as nor-adrenaline and/or adrenaline. However, there is evidence that addition of adrenaline and/or nor-adrenaline may aggravate the conditions for some organs, and there is a
10 tendency in the art to avoid the addition of catecholamines. Traditionally, dopamine has been the inotrope of choice in doses titrated to ensure cardiac output and vasoconstriction to ensure perfusion pressure gradients to the myocardium and the renal circulation.

Catecholamines have a half-life of approximately a few minutes when circulating in blood. Normal secretion in the adrenal medulla of adrenaline is 0.2 µg/kg/min and of nor-
15 adrenaline 0.05 µg/kg/min.

It is reported in the literature that administration of nor-adrenaline has been associated with myocardial damage and initial nonfunctioning after cardiac transplantation. It is hypothesized that the "catecholamine storm" after brain death may cause myocardial ischemia or rapid desensitization of the beta-adrenergic signaling pathway. Administration of
20 further nor-adrenaline after brain death may further desensitize the myocardial beta-adrenergic signaling.

Another possible explanation might be that, under massive catecholamine release, the uptake and inactivation/metabolization systems may be saturated, resulting in a down-regulation of beta adrenergic cardiac receptors (BAR), i.e. a reduction of BAR density, which
25 may be dose dependent. The recovery potential of BAR remains unknown, but may have an impact on organ function.

In addition, catecholamines may sulfoconjugate, which is regarded as an inactivation process by which the organism "pools" free plasma catecholamines into inactivated derivatives, which subsequently are deconjugated and released.

30 Thus, there is evidence that high levels of catecholamines may impair the alpha- and/or beta-receptors potency. In addition, the elimination system may be saturated, which may finally result in poor graft outcome.

A fundamental idea of the present embodiments is to replace at least some of the substances and/or hormones that are no longer excreted, or are excreted in substantially lower
35 levels, by the brain dead body compared to a living body. The focus is to maintain hemodynamic stability by cardiovascular support because it may maintain all of the donor organs in the best possible condition.

The inventor has found that adrenaline and nor-adrenaline are two substances that would be beneficial to add, but the addition of either of the substances is controversial and may result in undesired side effects as mentioned above.

Although the exact mechanism is unknown today, it is believed that a high level of catecholamines, such as under the "catecholamine storm" will cause a depletion of the stores of catecholamine normally found in the nerve terminals and adrenal medulla. In addition, the vascular tonus is lost, because the nerve terminals receive no signals from the brain.

Nor-adrenaline is normally produced in the pre-synaptic nerve terminal from tyrosine, which is an amino acid present all over the body in large quantities.

Fig. 1 is a schematic and simplified view showing a nerve terminal of the sympathetic nerve system. The nerve terminal ends in a presynaptic adrenergic varicosity 11 having a cell membrane 12. A postsynaptic effector cell membrane 14 is positioned a short distance from the cell membrane 12. The distance is called the synaptic cleft and may be about 20 nm in a chemical synapse.

Tyrosine is transported into the varicosity 11 via a transporter 15 and into the cytoplasm, wherein the tyrosine is converted to DOPA under the influence of an enzyme; Tyrosine Hydroxylase (TH). This step is considered to be the rate-limiting step in the synthesis of nor-adrenaline and adrenaline.

DOPA is transformed to dopamine in the cytoplasm under the influence of an enzyme; Aromatic L-amino acid decarboxylase (AAADC).

Dopamine is taken up into vesicles 16 via an active transporter 17 called VMAT-2 (Vesicular Monoamine Transporter), which is relatively non-specific and can transport different catecholamines, such as nor-adrenaline and dopamine, and other substances. Only about 50% of the dopamine produced is normally transported into the vesicles 16; the rest is metabolized by an enzyme called MAO (Monoamine Oxidase), see further below. There are a great number of vesicles in the nerve terminal.

Inside the vesicle, there is an enzyme; Dopamine- β -hydroxylase (D β H), which converts the dopamine entering the vesicle into nor-adrenaline (NA). In addition, any nor-adrenaline present inside the varicosity 11 is transported into the vesicle 16 by the same transporter 17 VMAT-2. In this way, nor-adrenaline is reused. A portion of the nor-adrenaline inside the varicosity does not enter the vesicle 16 but is metabolized by the enzyme MAO. Thus, there is a competition between the enzyme MAO and the active transporter 17 VMAT-2, both with regard to dopamine and nor-adrenaline.

The concentration of nor-adrenaline inside the vesicle is very high. A concentration in the range of 1 mole/liter has been reported.

At depolarization of the nerve cell membrane at the arrival of a stimulation signal, several voltage dependent calcium ion channels 18 allow the passage of calcium ions through

the varicosity membrane 12. Elevated levels of calcium ions promote the fusion of vesicular membrane with the membrane of the varicosity with subsequent exocytosis of nor-adrenaline, NA. The fusion process involves the interaction of specialized proteins associated with the vesicular membrane (VAMPs, vesicle-associated membrane proteins) and the membrane of the varicosity (SNAPs, synaptosome-associated proteins). When the vesicle emits its content into the synaptic cleft, the nor-adrenaline passes into the synaptic cleft and may interact with alfa- and beta-receptors present at the effector cell membrane, as shown by arrows in Fig. 1. Since the concentration of nor-adrenaline in the vesicle is extremely high and because the concentration of nor-adrenaline in the synaptic cleft normally is very low, and because the distance across the synaptic cleft is very small, some 20 nm, the nor-adrenaline will more or less explode due to the high concentration gradient and rapidly reaches the receptors at the effector cell membrane. The entire process comprising receipt of a depolarization voltage, inflow of calcium and exocytosis of nor-adrenaline takes often less than 1/10:th of a second.

The released nor-adrenaline may also interact with presynaptic receptors of alfa-2-type and beta-type. The alfa-2-receptor may influence directly on the vesicle and diminish the release of nor-adrenaline. The beta-receptor may facilitate the release of nor-adrenaline. The mechanism is not clearly understood for such direct influence of the release of the nor-adrenaline.

After some time, nor-adrenaline attached to the receptors is released from the receptors in the synaptic cleft. The nor-adrenaline present in the synaptic cleft is transported into the adrenal varicosity by an active transporter 19, called NET (nor-epinephrine transporter, nor-epinephrine = nor-adrenaline). This transporter has a high affinity for nor-adrenaline. NET removes free nor-adrenaline from the synaptic cleft, often within 0.1 seconds. However, a small portion of the free nor-adrenaline in the synaptic cleft passes out to the surrounding interstitial fluid and subsequently to the blood circulation. Circulating nor-adrenaline is rapidly metabolized in the liver, normally within a few minutes.

Thus, most of the nor-adrenaline released during exocytosis is reused. A portion is lost to the circulation and a portion is lost inside the adrenergic varicosity due to metabolization by MAO before entering the vesicle 16. Such lost nor-adrenaline is replaced by newly produced nor-adrenaline from tyrosine as explained above.

There is a negative feed-back regulation of the synthesis of nor-adrenaline from tyrosine. Thus, a high concentration of nor-adrenaline at the presynaptic alfa-2-receptors seems to decrease the production of nor-adrenaline, probably via interference with the rate-limiting enzyme TH.

The distance from the synaptic cleft to the blood circulation may be about 0.1 mm to several millimeters and is thus very much larger than the synaptic cleft. Thus, it takes long time for nor-adrenaline to diffuse from the synaptic cleft to the blood circulation and vice

versa. Consequently, the blood concentration of nor-adrenaline in a living human body is normally low. In addition, it takes a high concentration in the blood in order for some nor-adrenaline to diffuse to the synaptic cleft and influence upon the receptors of the effector cell membrane.

5 Adrenaline is produced from nor-adrenaline by an extra enzymatically driven step in the adrenal medulla. The enzyme is called phenylethanolamine N-methyltransferase (PNMT) and converts nor-adrenaline to adrenaline. This enzyme is present essentially only in the adrenal medulla. The adrenal medulla comprises nerve terminals similar to the adrenergic varicosity shown in Fig. 1 but lacks a postsynaptic portion. Instead, the exocytosis takes place
10 directly into the blood stream. Normally, the adrenal medulla excretes about 80% adrenaline and 20% nor-adrenaline into the blood.

 The above description is valid for a living body, such as the human being. When the body becomes brain dead, this condition is preceded by a catecholamine storm as explained above. Thus, as much nor-adrenaline as possible is released by exocytosis in the sympathetic
15 nerve system, causing increase of the vascular system resistance by means of the alfa-receptors of the effector cells. Consequently, all vesicles 16 in the nerve terminal are emptied into the synaptic cleft. Possibly, the uptake mechanism of the NET transporter 19 is overloaded and the concentration of nor-adrenaline in the synaptic cleft will increase, probably by a factor above 100. This will cause a disturbance of the reuse of nor-adrenaline
20 and the reuse of the vesicles after exocytosis. In addition, there will be a down-regulation of the release of the vesicles by the alfa-2-receptors. Furthermore, the new production of nor-adrenaline will be down-regulated by the high synaptic concentration of nor-adrenaline. Most of the produced nor-adrenaline will pass out into the blood circulation and be metabolized by the liver. Consequently, all stores of nor-adrenaline in the nerve terminals will be used up and
25 the operation of the nerve terminals will be severely disturbed.

 The adrenal medulla will also release all its storage of adrenaline as well as nor-adrenaline into the blood. The circulating catecholamines will be rapidly metabolized by the liver.

 Consequently, after the catecholamine storm, all stores of catecholamines,
30 particularly nor-adrenaline and adrenaline are exhausted. There is only a small new production of nor-adrenaline because the production from tyrosine takes several hours to adjust itself to the new situation.

 Thus, according to an embodiment of the present invention, adrenaline may be added in concentrations similar to those normally encountered in the blood. The added adrenaline
35 interacts with beta-receptors to promote for example cardiac output. Adrenaline has numerous other actions in the body as is well known to the skilled person.

According to another embodiment, nor-adrenaline may be added in concentrations sufficient to cause diffusion from the blood to the synaptic cleft and to the receptors present therein, normally alfa-receptors, in order to interact with for example alfa-receptors to cause vasoconstriction. Nor-adrenaline has numerous other actions in the body as is well known to the skilled person.

However, nor-adrenaline is normally produced and normally acts at sites different from the blood. This means that nor-adrenaline in the blood circulation may have a fast and direct effect at certain locations of the body, for example the kidney, while it may take longer time and have less effect at other locations, for example the vascular system. Thus, the consequence of adding nor-adrenaline to the blood circulation is very complex and incongruous.

One mechanism which may decrease the action of the nor-adrenalin circulating in the blood and diffusing to the synaptic cleft, may be the fact that any nor-adrenaline reaching the synaptic cleft will be rapidly taken up by the NET transporter and be entered into the presynaptic nerve terminal. Since the nerve terminal is depleted of nor-adrenaline, this action will be fast. Thus, the NET transporter will compete with the activation of the effector cell receptors and decrease the action of the added circulating nor-adrenaline. In order to obtain an effect, a high concentration of nor-adrenaline in the blood will be required, which is incompatible with other operations in the body.

If nor-adrenaline is added to the blood circulation, nor-adrenaline will be absorbed or soaked up by the nerve terminals. Thus, the state of depletion of the nerve terminals after the catecholamine storm may be reversed and normal operation of the nerve terminals may be resumed. However, because the brain dead body does not emit any nerve signals, the calcium channels remain unstimulated and no exocytosis and release of nor-adrenaline may take place.

The inventor has found that the addition of cocaine together with nor-adrenaline would permit the use of much lower levels of nor-adrenaline in the blood circulation and still obtain the desired effects of vasoconstriction. One hypothesis for explaining this result may be that the cocaine acts as NET inhibitor, which is previously known. By blocking the reuptake of the nor-adrenaline from the synaptic cleft, the NET transporter will no longer compete with the alfa-receptor and the nor-adrenaline diffusing from the blood to the synaptic cleft may cause the desired action. Other explanations may be relevant in combination.

In order to test this hypothesis, other NET inhibitors were tested, such as desipramine and imipramine, which both are known to be NET inhibitors. It was shown that similar results were obtained by these tricyclic antidepressants. However, cocaine has a much smaller half-life time of about 1 hour while imipramine has a half-life time of 12 hours and desipramine has a half-life time of 30 hours. It was also shown that Venlafaxine (half-life time of 5 hours)

had a similar effect. Thus, it seems that NET inhibition is at least desirable in order to potentiate the effect of blood circulation nor-adrenaline.

The conclusion is that a combination of NET inhibitors and nor-adrenaline would produce a synergetic effect in a brain dead, respiration body, in order to maintain or increase the vascular resistance and potentiate the effect of blood circulating nor-adrenaline.

At least a combination of nor-adrenaline and tricyclic antidepressants (including cocaine) would have the synergistic effect.

The same substances also have influence upon the action of adrenaline in the brain-dead, respiration body. A hypothesis is that the tricyclic antidepressants have similar effect on beta-receptors as has cocaine, for example to prevent down regulation of beta adrenergic cardiac receptors (BAR), i.e. a reduction of BAR density, see above.

Typical NET inhibitors are the following substances:

Tertiary Amine Tricyclics, such as: Amitriptyline (ELAVIL), Clomipramine (ANAFRANIL), Doxepin (ADAPIN, SINEQUAN), Imipramine (TROFANIL), Trimipramine (SURMONTIL);

Secondary Amine Tricyclics, such as: Amoxapine (ASENDIN); Desipramine (NORPRAMIN); Maprotiline (LUDIOMIL); Nortriptyline (PAMELOR); Protriptyline (VIVACTIL);

Venlafaxin (EFFEXOR); Atomoxetine (WELLBUTRIN); Duloxetine (CYMBALTA); Mirtazapine (REMERON); Norclomipramine; Oxaprotiline; Lofepramine, Reboxetine, Maprotiline, Nomifensine, Doxepin, Mianserin, Viloxazine, Mirtazapine, Nisoxetine and cocaine.

The potency seems to be highest for Desipramine, Protriptylin and Norclomipramine.

In one embodiment, cocaine (benzoylethyl ecgonine) has been used. Cocaine acts as a NET inhibitor of nor-adrenaline and dopamine. The neuronal terminals will be protected from the high systemic levels of catecholamines. The level of catecholamines in the circulating blood may be maintained by infusion of small amounts of adrenaline and/or nor-adrenaline. Thus, the neuronal action will be preserved in spite of exposure for high levels of circulating catecholamines both during the "storm" and subsequently during the next 24 hours before harvesting of the organs. By the addition of adrenaline and/or nor-adrenaline, the sympathetic and parasympathetic tones may be maintained, preventing for example uncontrolled vasodilatation and tachycardia.

Cocaine and NET inhibitors may also or alternatively act via further mechanisms not known today, and may have a beneficial effect for preserving organs before harvesting in a brain dead, respiration body.

Cocaine analogues may operate in the same way. Analogues may be any analogue as defined above. It is believed that it is the stimulant effect of cocaine that is active. Thus, cocaine analogues mean cocaine analogues with stimulating effect.

Cocaine-analogues with both stimulant & local anesthetic effects are: Dimethocaine or larocaine (DMC) ((3-diethylamino-2,2-dimethylpropyl)-4-aminobenzoate); and 3-(p-Fluorobenzoyl)tropane ((1R,5S)-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-fluorobenzoate).

Cocain-analogues for stimulant effects with local anesthetic effects removed are: β -CIT (methyl (1R,2S,3S,5S)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate); β -CPPIT (3 β -(4'-Chlorophenyl)-2 β -(3'-phenylisoxazol-5'-yl)tropane); FE- β -CPPIT (N-(2'-Fluoroethyl)-3 β -(4'-chlorophenyl)-2 β -(3'-phenylisoxazol-5'-yl)nortropane); FP- β -CPPIT (N-(3'-Fluoropropyl)-3 β -(4'-chlorophenyl)-2 β -(3'-phenylisoxazol-5'-yl)nortropane); Altropane (methyl (1R,2S,3S,5S)-3-(4-fluorophenyl)-8-[(E)-3-iodoprop-2-enyl]-8-azabicyclo[3.2.1]octane-2-carboxylate); Brasofensine ((E)-1-[(1R,2R,3S,5S)-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]-N-methoxymethanimine); CFT (methyl (1R,2S,3S,5S)-3-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate); Dichloropane (methyl (1R,2S,3S,5S)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate); Difluoropine (methyl (1S,2S,3S,5R)-3-[bis(4-fluorophenyl)methoxy]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate); Ioflupane (¹²³I) (methyl (1R,2S,3S,5S)-3-(4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate); Nocaine (methyl (3R,4S)-4-(4-chlorophenyl)-1-methylpiperidine-3-carboxylate); Tesofensine ((1R,2R,3S,5S)-3-(3,4-dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-azabicyclo[3.2.1]octane); Troparil (methyl (1R,2S,3S,5S)-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate); Tropoxane (methyl (1R,2S,3S,5S)-3-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane-2-carboxylate); (-)-Methyl-1-methyl-4 β -(2-naphthyl)piperidine-3 β -carboxylate (methyl (3S,4S)-1-methyl-4-naphthalen-2-ylpiperidine-3-carboxylate); PIT (2-Propanoyl-3-(4-isopropylphenyl)-tropane); PTT (2 β -Propanoyl-3 β -(4-tolyl)-tropane); RTI-121, IPCIT (propan-2-yl (1R,2S,3S)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate); RTI-126 ((1R,2S,3S,5S)-8-methyl-2-(1,2,4-oxadiazol-5-methyl)-3-phenyl-8-azabicyclo[3.2.1]octane); RTI-150 (cyclobutyl (1R,2S,3S,5S)-8-methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate); RTI-336 ((1R,2S,3S,5S)-8-methyl-2-(3-(4-methylphenyl)isoxazol-5-yl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octane); WF-23 (2 β -Propanoyl-3 β -(2-naphthyl)-tropane); WF-33 (2 α -(Propanoyl)-3 β -(2-(6-methoxynaphthyl))-tropane).

The use of a cocaine analogue with the stimulating effect removed and including a local anesthetic effect cannot be used for the purpose of the present embodiments. Lidocaine is a typical example. However, infusion of Lidocaine will result in vasodilatation and a

lowering of the blood pressure. It is expected that other local anesthetic agents similar to Lidocaine will produce the same blood pressure lowering effect.

It has been found that by using a NET inhibitor, such as cocaine or a cocaine analogue (stimulating) or a tricyclic antidepressant, it is possible to maintain a brain-dead,
5 heart-beating, respirated donor for 24 hours, with substantial maintenance of organ viability, by intravenous injection of the NET inhibitor and nor-adrenaline.

In particular, the heart will benefit by the NET inhibitor, which seems to decrease the cardiac irritability.

In addition, it has been found that pulmonary edema may decrease by the use of a
10 NET inhibitor. This will improve the result of subsequent pulmonary transplantation.

By further addition of small amounts of a vasopressor agent, the operation of the kidney can be maintained and the outcome of kidney transplantation is expected to improve.

The same is true for the liver and other organs, such as pancreas, intestines, etc. This may be caused by the improved cardiovascular stability obtained.

15 The body is provided with proper respiratory ventilation to keep the partial pressures of oxygen and carbon dioxide at suitable levels. Normally the brain dead body has no spontaneous respiration, which means that active ventilation is required. Such ventilation may take place in any manner previously known, for example by a respirator, by external compression of thorax, by manual or mechanical means, etc.

20 The body is also provided with an infusion solution for maintaining fluid balance. The kidneys produce urine at a desired output level of at least 1.0 ml/kg/hour. Thus, a fluid, such as Krebs's Ringer's solution, is infused at a rate of about 1 to 5 ml/kg/hour to compensate for kidney output, sweat and fluid losses during respiration.

25 The composition may further contain additional components such as cortisone, thyroxin (T4), insulin, triiodotyronine (T3), a vasopressor agent, such as arginine vasopressin, desmopressin or Minirin, and methylprednisolone (cortisone).

In order to avoid diabetes insipidus, it may be proper to add desmopressin already as early as possible, for example a bolus at the start of the intervention and then a normal continuous dose as produced by the body. Desmopressin may be titrated in dependence of the
30 urine output, in order to maintain the goal of for example 1.0 ml/kg/hour. Since the urine output immediately after the catecholamine storm is very small or even non-existent, it may be required to add a Diuretic agent, such as Furosemide (LASIX) in order to start urine production.

35 In one example the composition comprises the NET inhibitor, such as cocaine, and in addition adrenaline, nor-adrenaline, cortisone, thyroxin, triiodotyronine, and desmopressin.

The ratio between the NET inhibitor:nor-adrenaline may be about 1:1.

In some embodiments, the adrenaline and/or nor-adrenaline may be partly or entirely replaced by an equivalent substance. For example, phenylephrine is an alfa-1-agonist and may replace nor-adrenaline. It seems that phenylephrine is about 5 times less potent as nor-adrenaline.

5 Dopamine may be added in quantities less than about 0.01 mg/kg/min.

The embodiments also relate to an infusion solution comprising the composition as defined above dissolved in a pharmaceutical acceptable medium. Examples of acceptable mediums are physiological sodium chloride solution, Hartmann's solution and Ringer's (acetate) solution. Since the added volume is very small, in the range of 1.7 ml/hour (=0.04
10 ml/kg/hour), the ingredients may be dissolved in sterile, non-ionic water, i.e. pure H₂O.

The final amounts of the different components, which may be present in the infusion solution of a volume of 50 ml, are about 0.1 to about 10 mg of nor-adrenaline, for example 1 mg, 0.1 to about 10 mg of adrenaline, such as 1 mg, 0.1 to about 10 mg of the NET inhibitor, such as 1 mg. The other components, which may be present, may be in an amount of
15 about 0.05 to about 3 mg of triiodotyronine, T3, about 100 to about 1000 mg hydrocortisone, insulin and desmopressin.

EXPERIMENT 1

The following ingredients: 1 mg (1ml) adrenaline, 1 mg (1 ml) nor-adrenaline, 0.3
20 mg (3 ml) T3, 300 mg (3 ml) cortisone, 36 mg (9 ml) Minirin and 1 mg (3 ml) cocaine were dissolved in 50 ml physiological sodium chloride solution. The solution was added to the brain-dead, heart-beating cadaver of a pig with a weight of 40 kg, by intravenous infusion at an initial rate of 1.7 ml/hour, which was subsequently decreased in a dose dependent manner in order to maintain the mean arterial pressure MAP above about 60 mmHg. The infusion rate
25 could be reduced to about 0.4 ml/hour over 24 hours.

In order to maintain blood volume, Macrodex replacement fluid was added at 100 ml/hour (2.5 ml/kg/hour) to support a urine output of about 1.9 liters over 24 hours. The rest of the added fluid is removed from the body via lung respiration and sweat.

In order to counteract any tendency to form edema or any vascular instability, it may
30 be proper to add dextran to the replacement fluid, such as Dextran 40 or Dextran 70.

For reducing the risk of diabetes insipidus, a bolus of 12 mg Minirin was given at the start of the treatment.

The cadaver showed no significant signs of organ dysfunction. The heart, lungs, liver, kidney, and other organs were proper for transplantation purpose.

35 The blood pressure in an experiment with the above solution at a pig with a weight of 40 kg is shown in Fig. 1. The upper curve is the systolic pressure, the middle curve is the

calculated mean arterial pressure MAP and the lower curve is the diastolic pressure. The ordinata shows the blood pressure in mmHg and the abscissa shows the time in hours.

After 14 hours, the infusion rate was increased, resulting in a clear and immediate increase of blood pressure. The infusion rate was then lowered to obtain base-line pressures. As is shown in Fig. 1, the MAP was maintained at 80 mmHg, which is sufficient for keeping all organs well perfused of blood.

During the harvesting of the organs after 24 hours, the infusion of the solution was again increased to baseline of 1.7 ml/hour during half an hour before harvesting and maintained until all organs were removed.

An infusion rate of 1.7 ml/hour corresponds to an infusion of 0.015 µg/kg/min of adrenaline and nor-adrenaline, which is less than the normal production rate of the adrenal medulla, which may be about 0.05 µg/kg/min. Such small infusion rate into the blood is believed to be tolerated by the organs and the system of the brain dead body.

EXPERIMENT 2

A similar experiment was conducted wherein cocaine was replaced by desipramine. 3 mg of desipramine was added instead of 1 mg cocaine to 50 ml of physiological sodium chloride solution. In addition 1 mg of adrenaline and 1 mg of nor-adrenaline was included in the solution.

The desipramine solution was added to a pig similar to the pig in Experiment 1 at time instance 21 hours. The infusion rate was 1.7 ml/hour. The infusion rate was increased to 3.2 ml/hour at time instance 22 hours and the blood pressure started to rise. At time instance 26 hours, the infusion rate was decreased to 2.5 ml/hour. At time instance 28 hours, the infusion rate was decreased to 1.7 ml/hour.

The blood pressure during the time interval from 17 hours to 35 hours is shown in Fig. 3. In the same way as Fig. 2, the upper curve is the systolic blood pressure, the middle curve is the calculated mean arterial pressure MAP and the lower curve is the diastolic pressure. In addition, the mean pulmonary pressure is shown at the bottom curve.

As can be seen, the brain-dead body answered on the infusion of desipramine by increasing the blood pressure from a mean pressure of about 40 mmHg to a mean pressure of 80 mmHg. When the infusion rate was decreased, the blood pressure went down to about 60 mmHg, but never decreased further. It is believed that desipramine maintained its NET inhibitory effect over a long time because of its long half-life time. Thus, desipramine was active even when the infusion of desipramine was decreased and for several hours thereafter.

The infusion solution comprising the substances mentioned above is added to the blood circulation intravenously. The addition takes place by means of an electronically controlled infusion pump as shown in Fig. 5.

Fig. 5 shows an infusion kit according to an embodiment. The kit comprises a bag 21 for maintaining the infusion solution. The bag may comprise a volume of 50 ml of infusion solution. A tube 22 connects the bottom of the bag 21 with an infusion pump 23, which may be a syringe provided with an electric motor for automatic operation. A peristaltic pump operating on the tube 22 may alternatively be used. A second tube 24 connects the pump with a needle 25 intended to be introduced into a vein of a brain-dead, heart-beating, respiration potential donor. Alternatively, any type of access or connection to the vascular system may be used, such as a venous catheter. Since the volume to be infused over several hours is only about 50 ml, a large syringe may replace the bag and the pump.

In another embodiment, the volume of infusion solution is about 100 ml, which will be sufficient for a large patient of up to 100 kg during 24 hours. In this case, the entire procedure may take place fully automatically, without any need for manual intervention.

Fig. 6 discloses several infusion bags 31, 41, 51, 61, 71 and 81. The bags are the same as the corresponding bag 21 of Fig. 5. Six bags are shown in Fig. 6, but there may be any number of bags as required. A tube 32, 42, 52, 62, 72, 82 connects the bottom of the bag with an infusion pump 33, 43, 53, 63, 73, 83 which may be a syringe or a peristaltic pump. A second tube 34, 44, 54, 64, 74, 84 connects the pump with a needle 35 intended to be introduced into a vein of a brain-dead, heart-beating, respiration potential donor. A common tube 36 connects each end of the second tube to the needle 35.

Each bag may comprise one or several of the ingredients mentioned above. For example, bag 31 may comprise adrenaline, bag 41 may comprise nor-adrenaline, bag 51 may comprise cocaine or a NET inhibitor, bag 61 may comprise Minirin, bag 71 may comprise a mixture of hormones, such as T3, T4, cortisone, etc, and bag 81 may comprise an infusion solution such as Krebs-Ringer solution, which is an isotonic infusion solution comprising glucose.

Each pump may be controlled by a computer 90 as shown in Fig. 6. The computer receives input signals from sensors 91, 92, 93 etc. For example, pump 33 may be controlled in dependence of the cardiac output, for controlling addition of adrenaline, pump 43 may be controlled in dependence of the blood pressure or vascular resistance for controlling the addition of nor-adrenaline, pump 53 may be controlled in dependence of the effect of adrenaline and/or nor-adrenaline or may be controlled according to a desired predetermined control strategy, pump 63 may be controlled in dependence of the the urine output, pump 73 may be controlled according to a desired control strategy and pump 83 may be controlled for balancing the fluid loss via urine, sweat and respiration.

The computer may operate according to several strategies. One strategy may be to add cocaine at a rate which is proportional to the addition rate of nor-adrenaline. Another strategy may be to add cocaine in proportion to the addition rate of adrenaline or the sum of adrenaline and nor-adrenaline. A further strategy would be to add cocaine in a constant rate independent of the addition of adrenaline and/or nor-adrenaline.

If another NET inhibitor is used having a long half-life, a bolus at the start of the intervention would be adequate, followed by a smaller bolus after six hours etc. The effect of the bolus will be present during a long time after the bolus injection and the hemodynamic stability can be controlled by small amounts of adrenaline and nor-adrenaline.

The treatment or intervention should start as soon as possible after determination of brain death. There may be time delays between the actual death and the time when the condition of brain death is determined and such time delays should be as short as possible. The treatment may start with a bolus injection, especially if there is a substantial time delay and the blood pressure already is below about 50 mmHg.

The treatment is continued as until it is determined that organ harvesting should be performed. Shortly before harvesting, the infusion is increased to prepare the organs for maintaining as proper condition as possible during harvesting and the time immediately following harvesting. The treatment is performed from immediately after brain death until organ harvesting.

The inventor has performed more than 20 experiments with pigs and using cocaine in combination with adrenaline and nor-adrenaline. In each case it has been possible to maintain the blood pressure at a constant level of for example 70 mmHg from the initiation of the intervention and over 24 hours. Usually, the dose required during the first hours has to be reduced, for example from 1.7 ml/hour during the first six hours and down to 0.4 ml/hour during the last six hours. However, there are large individual differences. By this action, the blood pressure immediately after the catecholamine storm can be maintained at a sufficient level, thereby avoiding a blood pressure below 40 mmHg, which normally occurs after the catecholamine storm if no intervention is performed.

In many cases, it is not required to control all parameters and use six (or more) individually controlled supplies. One versatile combination would be to have adrenaline and cocaine in bag 31, nor-adrenaline and cocaine in bag 41, Minirin in bag 51, infusion solution in bag 61 and the other ingredients in bag 71, and excluding bag 81.

A further embodiment would include adrenaline, nor-adrenaline and cocaine in bag 31, further ingredients in a second bag 41 and infusion solution in a third bag 51.

Alternatively, both the infusion solution, which comprises a NET inhibitor, and the replacement fluid may be arranged in the same bag, which in this case should have a volume of about 2.5 liter.

The inventor has also found that other strategies than using a NET inhibitor may be used for achieving the desired feature that intravenous infusion of nor-adrenaline may be used, separately or in combination.

Thus, it is known that amphetamines may increase or potentiate the effect of nor-adrenaline in the synaptic cleft. The mechanism is different than NET inhibitors.
Amphetamine competes with nor-adrenaline at the NET transporter 19 and particularly at the VMAT-2 transporter into the vesicles 16. Thus, amphetamine present in the synaptic cleft may enter the adrenergic varicosity 11 via a NET transporter 19. However, in-transport of amphetamine facilitates out-transport of nor-adrenaline. In addition, amphetamine enters the vesicle 16 and displaces nor-adrenaline out from the vesicle. The nor-adrenaline outside the vesicle in the axoplasm inside the varicosity is exposed to metabolism by MAO. However, amphetamine also acts as a MAO inhibitor, and at least partly decrease metabolism of nor-adrenaline. Thus, nor-adrenaline present in the axoplasm may be out-transported via the NET transporter 19 as a result of in-transport of amphetamine. The net result is that the concentration of nor-adrenaline increases in the synaptic cleft resulting in a potentiation of the interaction with effector cell receptors, such as alfa- and beta-receptors.

In the situation present after brain death, the conditions are different compared to that explained above. The nor-adrenaline present in the adrenergic varicosity and the vesicles has been depleted by the massive exocytosis during the catecholamine storm. Thus, there is substantially no nor-adrenaline that can be displaced by the action of amphetamine. During the initial time after the catecholamine storm, the main effect of amphetamine will be to compete with nor-adrenaline for the NET transporter and partly block reuptake by the NET transporter of nor-adrenaline.

If cocaine is administered at the same time as amphetamine, the amphetamine will have substantially no action, since cocaine is blocking not only in-transport of nor-adrenaline but also in-transport of amphetamine by the NET transporter.

However, after some time, the nerve terminals have partly recovered and comprise nor-adrenaline inside the adrenergic varicosity in the vesicles, either newly synthesized or in-transported via the NET transporter. However, there is substantially no exocytosis, since the nerves do not receive any nerve impulses that open the calcium channels for influx of calcium. In this situation, amphetamine will have the effect that nor-adrenaline inside the vesicles will be displaced out to the axoplasm of the varicosity and further out to the synaptic cleft via out-transport via the NET transporter, under the influence of amphetamine. In addition, amphetamine will slow down the metabolism of nor-adrenaline in the axoplasm inside the varicosity by MAO inhibition. Consequently, the nerve terminal will, under the influence of amphetamine "leak" some nor-adrenaline, which will maintain the tonus of the vascular system.

To summarize, in a brain dead potential donor body, amphetamine has a first potentiating effect of intravenous administration of nor-adrenaline by blocking uptake of nor-adrenaline in the synaptic cleft by NET transporters. In addition, a second effect is that amphetamine will promote leakage of nor-adrenaline from the nerve terminals, which will replace a lack of nerve impulses from the dead brain. The second effect will be more pronounced a few hours after the catecholamine storm when the production of nor-adrenaline has recovered.

A strategy for maintaining the hemodynamic stability of a brain dead body may be to infuse, by intravascular infusion, nor-adrenaline and amphetamine as early as possible after brain death. The infusion solution may further comprise adrenaline and all other ingredients mentioned above, except the NET inhibitor.

In particular, amphetamine interacts with adrenaline in a complex manner, which is expected to have beneficial effects.

Another strategy for maintaining the hemodynamic stability of a brain dead body may be to infuse, by intravascular infusion, nor-adrenaline and the NET inhibitor (for example cocaine) during an initial time period and then replace the NET inhibitor by amphetamine after a few hours, such as after three hours.

A further strategy would be to infuse a bolus of the NET inhibitor in order to enhance the action of nor-adrenaline, followed by administration of amphetamine. If the bolus is a substance having long half-time, such as tricyclic antidepressants, the bolus will have decreased its action when the amphetamine second action is active. However, one or several initial boluses by cocaine would also be contemplated.

There are further substances that are amphetamine-like substances and have the same or similar effects as amphetamine. Such substances are for example Tyramine and Ephedrine and Methylphenidate.

There are several amphetamines (**alpha-methylphenethylamine**). Amphetamine is the parent compound of its own structural class, comprising a broad range of psychoactive derivatives. Substituted amphetamines are a chemical class of drugs, which have a phenethylamine core with a methyl group attached to the alpha carbon resulting in amphetamine along with additional substitutions. There is a large number of active derivatives of this class, for example methamphetamine, etc. It is expected that such derivatives may be used in the present embodiments. These agents are included within the expression amphetamine-like substances.

Fig. 4 is a diagram over blood pressure during an experiment similar to Experiment 1. However, the infusion solution used did not contain any cocaine but all the other ingredients. At time instance 29.5 hours, amphetamine was included in the infusion solution, and resulted

in an immediate increase of mean arterial pressure by about 15 mmHg. The mean arterial pressure was constant until the experiment was terminated at time instance 36 hours.

In the claims, the term "comprises/comprising" does not exclude the presence of other elements or steps. Furthermore, although individually listed, a plurality of means,
5 elements or method steps may be implemented by e.g. a single unit. Additionally, although individual features may be included in different claims or embodiments, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms "a", "an", "first", "second" etc do not preclude a
10 plurality. Reference signs in the claims are provided merely as a clarifying example and shall not be construed as limiting the scope of the claims in any way.

Although the present invention has been described above with reference to specific embodiment and experiments, it is not intended to be limited to the specific form set forth herein. Rather, the invention is limited only by the accompanying claims and, other
15 embodiments than those specified above are equally possible within the scope of these appended claims.

CLAIMS

1. A composition for intravascular administration for treatment of a brain-dead, heart-beating, respirated potential organ donor, comprising:

nor-adrenaline and an amphetamine or an amphetamine-like substance.

2. The composition according to claim 1, wherein the amphetamine-like substance is at least one of the substances included in the group comprising: Tyramine and Ephedrine and Methylphenidate.

3. The composition according to any one of the previous claims, further comprising at least one of: adrenaline, hydrocortisone, thyroxin, insulin, triiodotyronine, dopamine, a vasopressor agent, such as desmopressin, and methylprednisolone.

4. An infusion solution comprising the composition according to any one of claims 1 to 3 and a pharmaceutically acceptable medium, such as pure water, Ringer's acetate solution or physiological sodium chloride solution.

5. A method for treatment of a brain dead, heart-beating, respirated potential organ donor, comprising:

infusion of the infusion solution according to claim 4, in an amount sufficient for maintaining a mean arterial pressure of at least about 60 mmHg.

6. A kit for intravenous administration for treatment of a brain dead, heart-beating, respirated potential organ donor, comprising

an infusion bag (21) comprising an infusion solution according to claim 4; an infusion pump (23) for pumping the infusion solution to a needle (25) inserted into the vascular system of the donor for controlling the amount of infusion solution entered into the donor and tubings (22, 24) for interconnecting the bag, pump and needle.

7. The kit according to claim 6, comprising several sets of infusion bags (31 to 81), infusion pumps (33 to 83) and tubings (32 to 82; 34 to 84).

8. The kit according to claim 6 or 7, further comprising a computer (90) for controlling the pump or pumps, whereby the computer is operated according to a predetermined control strategy.

9. A method of infusing a solution into the circulation system of a brain dead, heart-beating, respirated potential organ donor, comprising:

determining that the donor is brain dead;

continuing or initiating respiration for oxygenation of the blood;

5 infusion of an infusion solution according to claim 4;

controlling the infusion, for example by means of a computer.

10. The method according to claim 9, comprising:

after determination that the donor is brain dead;

10 initially infusing a second infusion solution having a composition according to claim 4, in which the amphetamine or the amphetamine-like substance has been replaced by a NET inhibitor, such as cocaine;

after a predetermined time, terminating infusion of said second infusion solution and infusion of an infusion solution according to claim 4.

15

11. The method according to claim 9, comprising:

after determination that the donor is brain dead;

initially infusing a bolus of a NET inhibitor, such as a tricyclic antidepressant.

20

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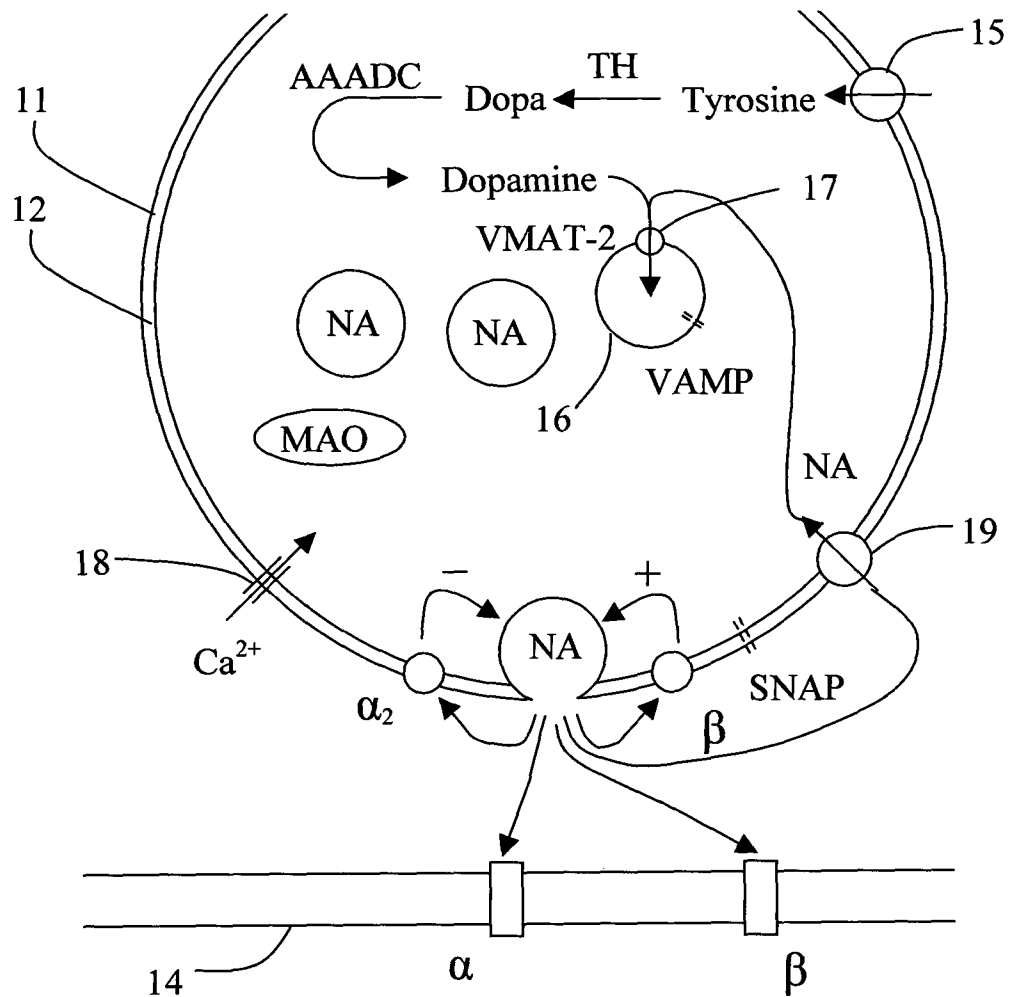


Fig. 1

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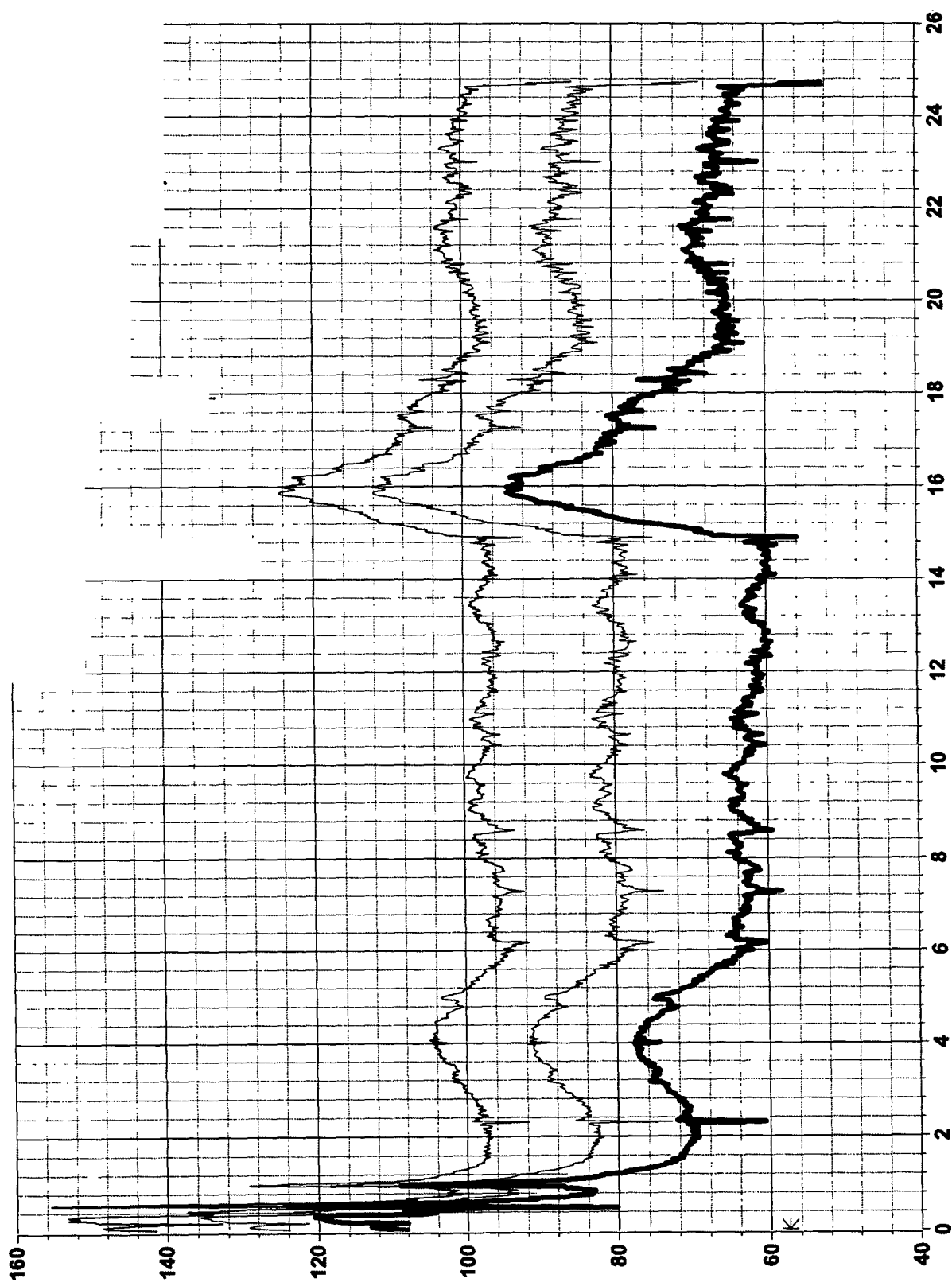


Fig. 2

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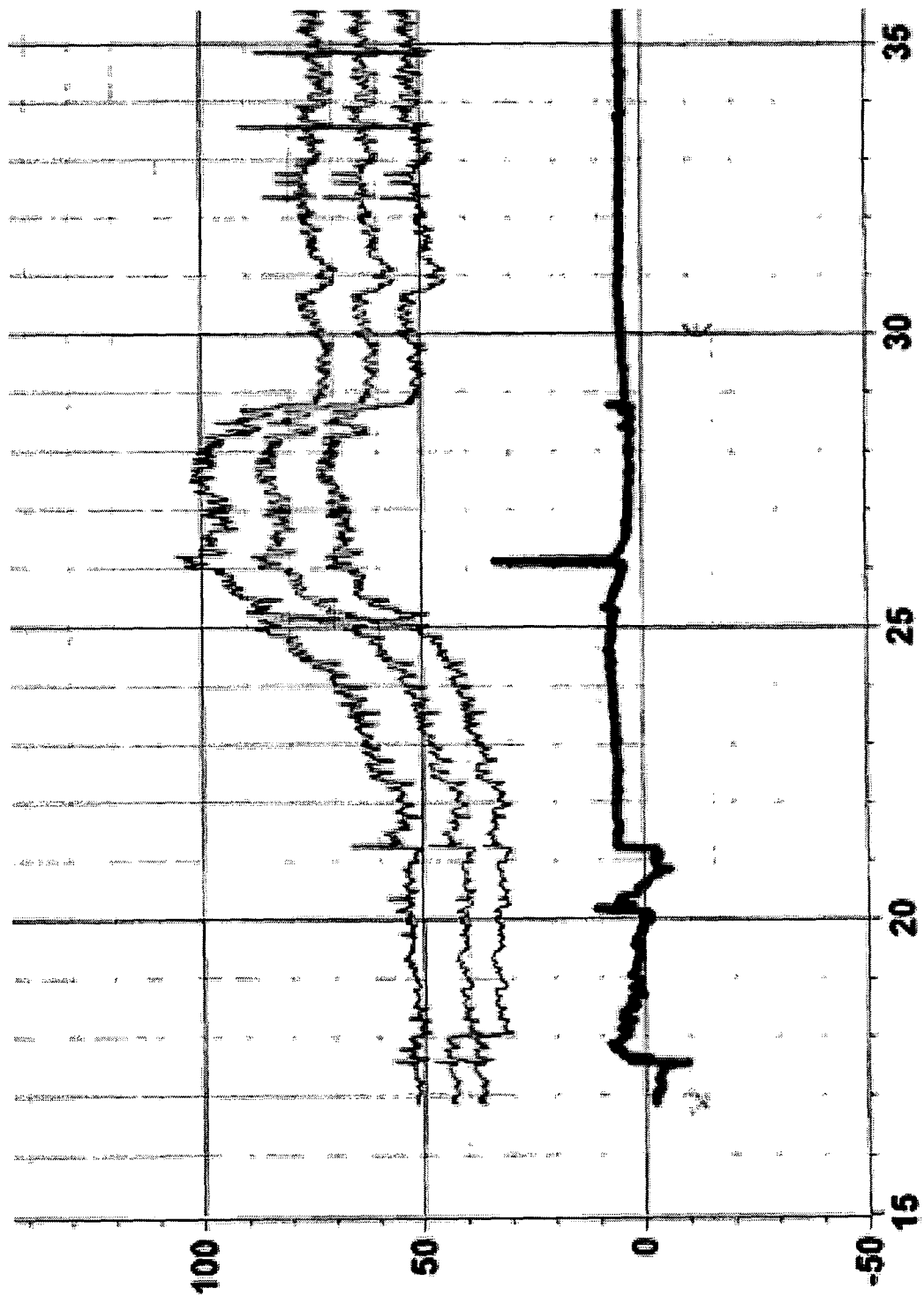


Fig. 3

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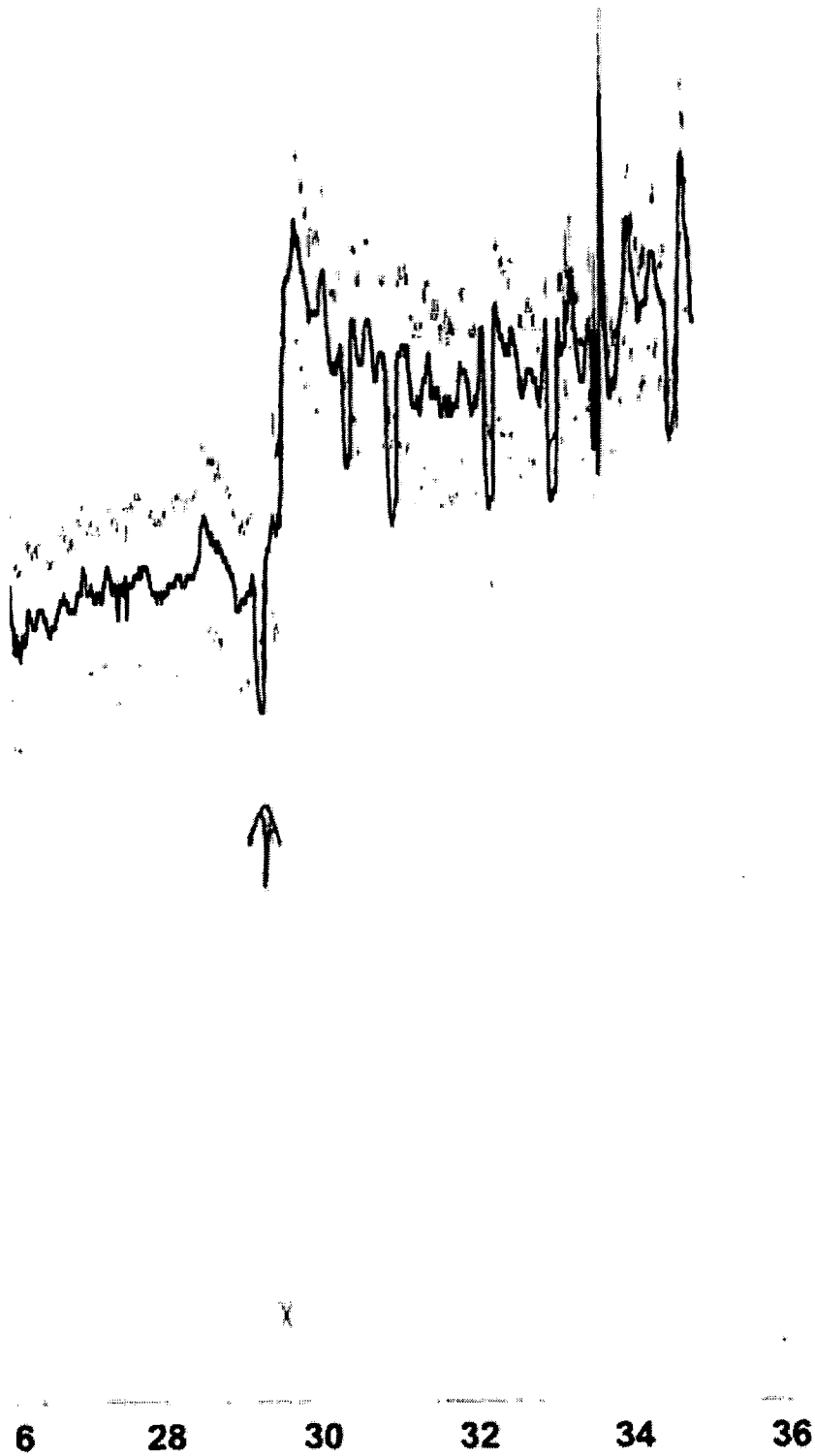


Fig. 4

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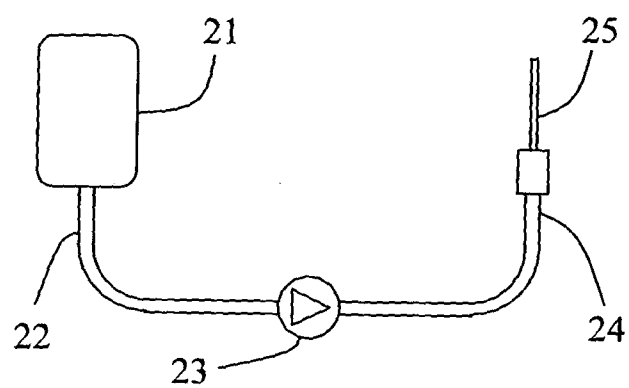
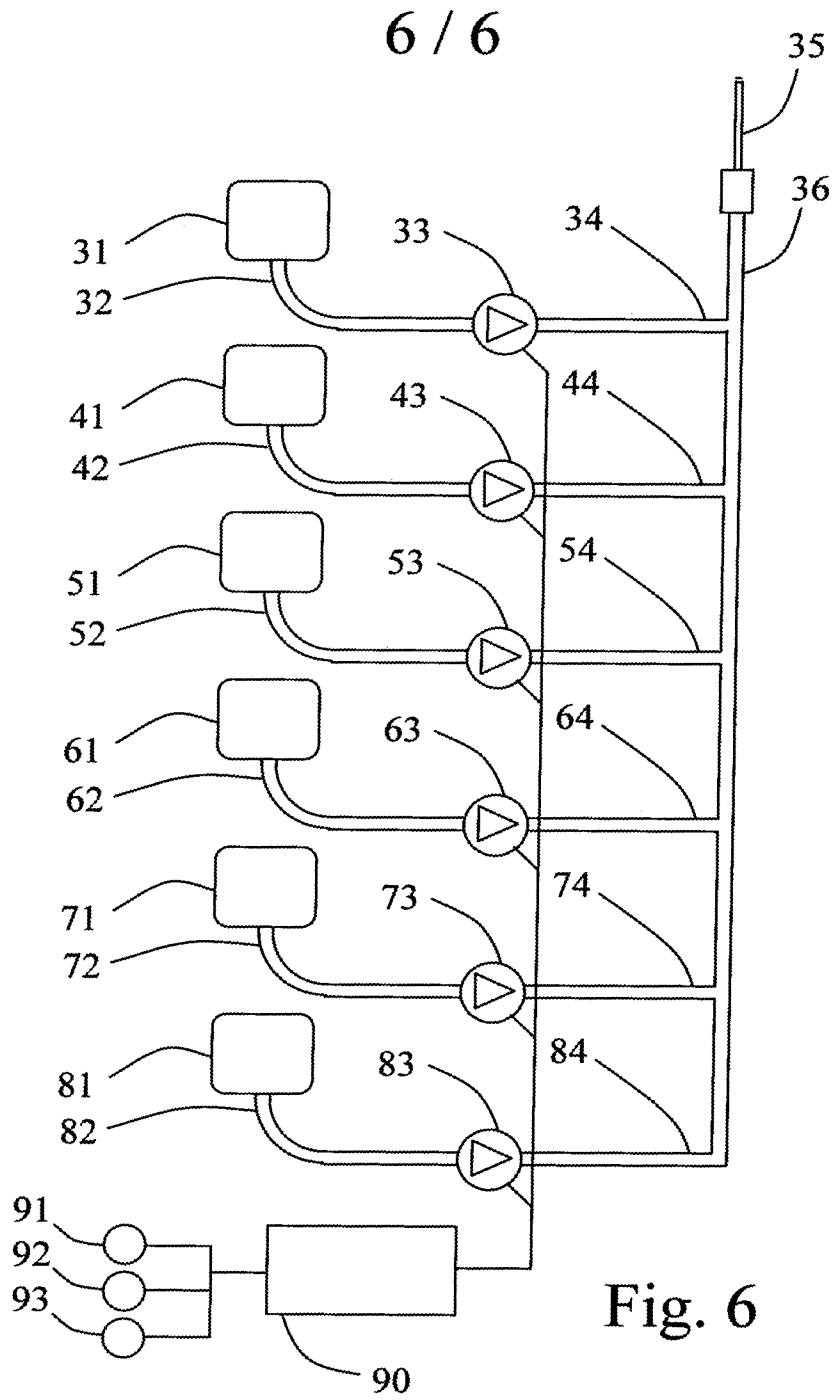


Fig. 5



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/000542

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: A01N, A61K, C07D

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, BIOSIS, MEDLINE, EMBASE, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BENTLEY, G. A. "The effect of local anaesthetic and anti-adrenaline drugs on the response of sympathetically innervated smooth muscle preparations to electrical stimulation at different frequencies". In: British Journal of Pharmacology and Chemotherapy, 1966, Vol. 27, pp. 64-80, page 65 --	1,4
A	SCHNUELLE, P., ET AL. "Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation". Ingår i: Kidney International, 1999, vol. 56, s. 738-746, the whole document --	1-11

☒ Further documents are listed in the continuation of Box C.☒ 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 application or patent 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

7 April 2010

Date of mailing of the international search report

13-04-2010

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/000542

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHULAK, J. A., ET AL. "Donor pretreatment with lidocaine decreases incidence of early renal dysfunction in cadaver kidney transplantation". Ingår i: Transplantation Proceedings, 1990, vol. 22, nr. 2, s. 353-354, the whole document --	1-11
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International patent classification (IPC)

A01N 1/02 (2006.01)
A61K 31/135 (2006.01)
A61K 31/137 (2006.01)
A61K 31/198 (2006.01)
A61K 31/46 (2006.01)
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A61K 38/11 (2006.01)

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