MACHINE PERFUSION SOLUTION FOR ORGAN AND BIOLOGICAL TISSUE PRESERVATION

Field of Invention

The invention relates to the field of organ and biological tissue preservation. In particular, the invention relates to machine perfusion solutions for the preservation of organs and biological tissues for implant.

Background of Invention

It is believed that the ability to preserve human organs for a few days by cold storage after initial flushing with an intracellular electrolyte solution or by pulsatile perfusion with an electrolyte-protein solution has allowed sufficient time for histo-compatibility testing of donor and recipient. It is also believed that preservation by solution or perfusion has also allowed for organ sharing among transplant centers, careful preoperative preparation of the recipient, time for preliminary donor culture results to become available, and vascular repairs of the organ prior to implantation.

It is believed that the 1990's has been a decade characterized by increasing waiting times for cadaveric organs. In renal transplantation, the growing disparity between available donors and patients on the waiting list has stimulated efforts to maximize utilization of cadaveric organs. An obstacle that may arise in the effort to increase utilization is that maximal utilization may require transplantation of all available organs, including extended criteria donor organs. However, by extending the criteria for suitability of donor organs, transplant clinicians may risk a penalty with respect to graft function, diminishing the efficiency of organ utilization if transplanted organs exhibit inferior graft survival. Consequently, interventions that both improve graft function and improve the ability of clinicians to assess the donor organ may be crucial to achieving the goal of maximizing the efficiency of cadaveric transplantation.

The mechanisms of injuries sustained by the cadaveric renal allograft during pre-preservation, cold ischemic preservation and reperfusion are believed to be complex and not fully understood. However, it is believed that there exists ample evidence to suggest that many of the injurious mechanisms occur as a result of the combination of prolonged cold ischemia and reperfusion (I/R). Reperfusion alone may not be deleterious to the graft, since reperfusion after short periods of cold ischemia may be well-tolerated, but reperfusion may be necessary for the manifestation of injuries that originate during deep and prolonged hypothermia. It is suggested that four major components of I/R injury that affect the

preserved renal allograft begin during cold ischemia and are expressed during reperfusion. These include endothelial injury, leukocyte sequestration, platelet adhesion and increased coagulation.

Hypothermically-induced injury to the endothelium during preservation may lead to drastic alterations in cytoskeletal and organelle structures. During ischemic stress, profound changes in endothelial cell calcium metabolism may occur. These changes may be marked by the release of calcium from intracellular depots and by the pathological influx of calcium through the plasma membrane. Hypothermic preservation may disrupt the membrane electrical potential gradient, resulting in ion redistribution and uncontrolled circulation of Ca++. The depletion of ATP stored during I/R may compromise ATP-dependent pumps that extrude Ca++ from the cell and the energy intensive shuttle of organelle membranes, causing a dramatic elevation of intracellular free Ca++.

Alterations in cytosolic Ca++ concentration may disrupt several intracellular functions, many of which may result in damaging effects. Unregulated calcium homeostasis has been implicated in the development of endothelial and parenchymal injury and is believed to be a fundamental step in the sequelae of steps leading to lethal cell injury. Among the most significant damaging effects of increased cytosolic Ca++ are believed to be the activation of phospholipase A1, 2 and C, the cytotoxic production of reactive oxygen species by macrophages, the activation of proteases that enhance the conversion of xanthine dehydrogenase to xanthine oxidase, and mitochondrial derangements.

Solutions for preserving organs are described in U.S. Patent Nos. 4,798,824 and 4,879,283, the disclosures of which are incorporated herein in their entirety. Despite such solutions, it is believed that there remains a need for organ and tissue preserving solutions that allow for static storage and preservation, while demonstrating superior quality preservation of organ and tissue viability and function.

Summary of the Invention

The invention provides an organ and tissue preserving solution for machine perfusion preservation that demonstrates superior quality preservation when compared to existing preserving media, in terms of organ and tissue viability and function. The organ and biological tissue preservation aqueous machine perfusion solution includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties, a nitric oxide donor, and a glutathione-forming agent.

The invention also provides a preserved organ and biological tissue. The preserved organ and biological tissue includes a cadaveric organ or tissue within the machine perfusion solution in a deep hypothermic condition or a physiological condition.

The invention also provides a perfusion machine comprising a chamber that mimics a deep hypothermic environment or physiological environment, where the machine perfusion solution continuously circulates through the chamber.

The invention also provides a method for preserving an organ or biological tissue. The method includes pouring the machine perfusion solution into a chamber that mimics a deep hypothermic environment or physiological environment, circulating the machine perfusion solution continuously through the chamber, inserting a cadaveric organ or tissue into the chamber, and flushing the cadaveric organ or tissue with the machine perfusion solution.

The invention further provides a method of preparing an organ or biological tissue machine perfusion solution. This method includes providing a solution with sterile water, adding sodium gluconate, potassium phosphate, adenine, ribose, calcium chloride, pentastarch, magnesium gluconate, HEPES, glucose, mannitol, and insulin to the solution, and mixing prostaglandin E1, nitroglycerin and N-acetylcysteine into the solution.

Detailed Description of the Invention

In accordance with the present invention, the organ and biological tissue preservation aqueous machine perfusion solution includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties, a nitric oxide donor, and a glutathione-forming agent. The organ and biological tissue preservation machine perfusion solution is intended for infusion into the vasculature of cadaveric and living donor organs for transplantation. Once infused, the donor

organs are exsanguinated and blood is replaced by the solution in the native vasculature of the organs to return the organs to a normothermic condition. The solution may be used under deep hypothermic conditions or physiological conditions. The solution remains in the vasculature of the organ as well as envelops the entire organ during the period of cold ischemia. This method of preservation allows for the extended storage of organs, tissues, and all biological substances. When the organ or tissue is returned to normothermic conditions, the solution is replaced with blood or other physiologic media. Variations of this solution may also be used for cold storage solution preservation. The machine perfusion solution of the invention may be used in the same manner and for the same tissues and organs as known machine perfusion solutions.

A machine perfusion solution of the invention includes a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties. One such prostaglandin is Prostaglandin E1 (PGE1). PGE1 is an endogenous eicosanoid of the cyclooxygenase pathway and is utilized for its potent vasodilatory properties. In addition, PGE1 has cellular and organelle membrane stabilization properties, cryoprotective properties, and ability to prevent platelet aggregation upon the vascular endothelium post transplant. As such, PGE1 may inhibit neutrophil adhesion, inhibit neutrophil production of oxygen free radical species, counteract procoagulant activity after endothelial injury, and stabilize cell membranes. When used in vivo, PGE1 is metabolized almost instantaneously by first pass clearance through the lung, but during hypothermic conditions, PGE1 in the machine perfusion solution may remain vasoactive even after several hours.

A machine perfusion solution of the invention also contains a nitric oxide donor, such as nitroglycerin. Nitroglycerin is utilized in the solution because of its potent nitric oxide donation properties, its ability to dilate the venous vascular system and prevent vasospasm, and its ability to prevent complement activation upon transplant. Nitroglycerine is known to relax smooth muscle cells of the endothelium, scavenge free oxygen radicals during reperfusion, and prevent the production of such radicals during cold ischemia.

Compounds that form glutathione (glutathione-forming agents) are also components of a machine perfusion solution of the invention. One such compound is n-acetylcysteine. Glutathione (GSH) is synthesized from L-glutamate, L-cysteine, and glycine in 2 ATP-dependent reactions. The first reaction, known as catalyzed bygamma-glutamylcysteine synthetase, is effectively rate-limited by GSH feedback. The second involves GSH

synthetase, which is not subject to feedback by GSH. When GSH is consumed and feedback inhibition is lost, availability of cysteine as a precursor becomes the rate-limiting factor. As such, N-acetylcysteine is proposed to be the only glutathione precursor that can enter the cell freely. In addition, the constitutive glutathione-building properties of N-acetylcysteine help prevent the formation of free oxygen radicals generated during the preservation period and during reperfusion with a recipient's blood.

According to a preferred embodiment of the invention, an organ and biological tissue preservation cold storage solution containing PGE1, nitroglycerin, and N-acetylcysteine in the preserving solution significantly improves vascular resistance, vascular flow, and calcium efflux during the organ preservation period. The inhibition of calcium efflux over time in kidneys preserved by the proposed solution suggests that, in addition to vasoactive effects, an additional cytoprotective and cryoprotective effect may also be important in ameliorating ischemic injury. These improvements are substantiated ultrastructurally by improved appearance of mitochondria in proximal tubular cells compared to mitochondria from kidneys not exposed to the proposed solution.

A machine perfusion solution of the invention may also contain components typically used in known machine perfusion solutions. *See*, U. S. Patent Nos. 4,798,824 and 4,879,283. For example, other components that may be utilized in the solution include: sodium gluconate and Mg gluconate, which are impermeant anions that reduce cell swelling, KH_2PO_4, which provides acid-base buffering and maintains the pH of the solution, adenine, which is a precursor to ATP synthesis, and ribose, which reduces cell swelling during hypothermia. In addition, $CaCl_2$, which is a calcium-dependent mitochondrial function supplement, HEPES, which is an acid-base buffer, glucose, which is a simple sugar that reduces cell swelling and provides energy stores for metabolically stressed cell, and mannitol and pentastarch, which are oncotic supporters, may also be added. NaCl and KOH may also be used for acid-base buffering and maintenance of the pH of the machine perfusion solution.

In a preferred embodiment, the organ or biological tissue preservation machine perfusion solution includes, but is not limited to:

Table 1

COMPOSITION	AMOUNT IN 1 LITER
Sodium Gluconate	40-160mM
KH_2PO_4	10-50mM
Mg Gluconate	1-15mM
Adenine	1-15mM
Ribose	1-15mM
$CaCl_2$	0.1-2mM
HEPES	1-30mM
Glucose	1-30mM
Mannitol	10-100mM
Pentastarch	40-60g/L
Prostaglandin E1	100-10,000mcg/L
Nitroglycerin	1-15mg/L
N-Acetylcysteine	0.1-5mg/L
Sterile Water	700-900mL

In a more preferred embodiment, the organ or biological tissue preservation machine perfusion solution includes, but is not limited to:

Table 2

COMPOSITION	AMOUNT IN 1 LITER
Sodium Gluconate	60-100mM
KH_2PO_4	20-30mM
Mg Gluconate	3-8mM
Adenine	3-8mM
Ribose	3-8mM
$CaCl_2$	0.3-0.8mM
HEPES	8-15mM
Glucose	8-15mM
Mannitol	15-50mM
Pentastarch	45-55g/L
Prostaglandin E1	250-2,500mcg/L
Nitroglycerin	3-8mg/L
N-Acetylcysteine	0.5-2mg/L
Sterile Water	700-900mL

In a most preferred embodiment, the organ or biological tissue preservation machine perfusion solution includes, but is not limited to:

Table 3

COMPOSITION	AMOUNT IN 1 LITER
Sodium Gluconate	Approx 80mM
KH_2PO_4	Approx 25mM
Mg Gluconate	Approx 5mM
Adenine	Approx 5mM
Ribose	Approx 5mM
$CaCl_2$	Approx 0.5mM
HEPES	Approx 10mM
Glucose	Approx 10mM
Mannitol	Approx 30mM
Pentastarch	Approx 50g/L
Prostaglandin E1	Approx 500mcg/L
Nitroglycerin	Approx 5mg/L
N-Acetylcysteine	Approx 1mg/L
Sterile Water	Approx 800mL

A machine perfusion solution of the invention may be prepared by combining the components described above with sterile water, such as distilled and/or deionized water. For example, to prepare the solution, approximately 700-900mL, or preferably about 800 mL, of sterile water is poured into a one liter beaker at approximately room temperature. Although a one liter beaker is used in this example, any other container of any size may be used to prepare the solution, where the component amounts would be adjusted accordingly. In the most preferred embodiment, the following are added, in any order, to the solution and each is mixed until dissolved in the solution: approximately 80 mol/L sodium gluconate, approximately 25 mol/L potassium phosphate, approximately 5 mol/L adenine, approximately 5 mol/L of ribose, approximately 0.5 mol/L of calcium chloride, and approximately 50 g modified pentastarch. The modified pentastarch is a fractionated colloid mixture of 40-60 kDaltons in diameter and is modified by infusing the pentastarch under 3 atm of pressure through a dialyzing filter with a bore size of about 40-60 kDaltons. About 5 mol/L magnesium gluconate, approximately 10 mol/L HEPES, approximately 10 mol/L

glucose, and approximately 30 mol/L mannitol are also added, in any order, and mixed. Approximately 40 U of insulin is also added. Then, in a second step, approximately 1 mg of N-acetylcysteine, approximately 5 mg nitroglycerin, and approximately 500 mcg of modified prostaglandin E1 (PGE1) are added, in any order, to the solution. PGE1 is modified by centrifuging PGE1 under hypothermic conditions at 30K rpm and then filtering the resulting mixture through a 0.05 micro filter. The modified PGE1 has a half-life lengthened by a multiple of about 15. To adjust the pH of the solution to about 7.2-7.5, or preferably, 7.4 +/- 0.1, 5N KOH or NaOH is added, as needed. The first and second step may also be reversed.

The invention also provides a method for preserving an organ or biological tissue. The method includes pouring the machine perfusion solution into a chamber that mimics a deep hypothermic environment or physiological environment and moving the machine perfusion solution continuously through the chamber. The machine perfusion solution is infused in a mechanical fashion through the arterial or venous vascular system of cadaveric or living donor organs, or infused over or through an avascular biological substance in order to maintain organ or tissue viability during the ex vivo period. Preferred temperatures range from about 2-10°C in the deep hypothermic condition and are about 37°C, or room temperature, in the physiological condition. Use of this solution provides for the serial assay of solution over time to determine hydrostatic and chemical changes. These hydrostatic and chemical changes provide a mechanism to determine the functional viability of the organ or tissue once it has been returned to physiologic conditions.

The invention further provides a perfusion machine comprising a chamber that mimics a deep hypothermic environment or physiological environment, where the machine perfusion solution continuously moves through the chamber. Any perfusion machine that is known in the art may be used with the solution, including machines providing pulsatile, low flow, high flow, and roller flow perfusion. Typically, the perfusion machine includes a unit for the static monitoring or transportation of organs or biological tissues and a cassette, or chamber, used to circulate perfusate through the organs or biological tissues. A monitor displays pulse pump rate, perfusate temperature, systolic, mean, and diastolic pressure, and real-time flow. Once such machine is the RM3 Renal Preservation System manufactured by Waters Instruments, Inc.® As discussed above, preferred temperatures range from about 2-10°C in the deep hypothermic condition and are about 37°C, or room temperature, in the physiological condition.

The invention is further explained by the following of examples of the invention as well as comparison examples. In all of the examples, kidneys were procured from heart-beating donors and preserved in a laboratory by cold storage preservation. Randomization was accomplished as an open labeled, sequential analysis. All agents were added immediately prior to vascular flush.

Data Collected

The following donor, preservation, and postoperative recipient outcome data were collected for either Example 1 or Example 2: donor age (D age, years), final donor creatinine (D Cr, mg/dL), donor intraoperative urine output (U/O, mL), cold ischemic time (CIT, hours), perfusion time (PT, hours), perfusate [Na+] (mM/100g), perfusate [C1-] (mM/100g), perfusate [K+] (mM/100g), perfusate [Ca++] (mM/100g), perfusate pH, renal flow during MP (FL, mL/min/100g), renal resistance during MP (RES, mmHg/(mL/min/100g), recipient age (R age, years), recipient discharge creatinine (R Cr, mg/dL), initial length of recipient hospital stay (LOS, days), immediate graft function (IF, %) defined as urine production exceeding 2000 mL during the first 24 post-operative hours, delayed renal allograft graft function (DGF, %) defined as the need for dialysis within the first 7 days post-transplant, and present function (3 Mo or 1 Yr., %) defined as 3 month or one year post-operative graft status.

Method of Preservation

Kidneys were perfused *en bloc* at 4°C and at 60 beats per minute with either 1 liter of UW-MPS (Belzer-MPS, TransMed Corp., Elk River, MN), Belzer I-Albumin (Suny-Downstate, Brooklyn, NY), or the Machine Perfusion Solution (Storage) (MPS) of the invention. The Belzer solution, which is also the Control-Belzer solution, is described in U.S. Patent Nos. 4,798,824 and 4,879,283. The Albumin solution contained, per liter, 17.5 g sodium bicarbonate, 3.4g potassium dihydrogen phosphate, 1.5g glucose, 9g glutathione, 1.3g adenosine, 4.7g HEPES, 200K units penicillin, 8mg dexamethasone, 12mg phenosulphathelein, 40 units insulin, 150 mL serum albumin, and 1g magnesium sulfate. In each of the solutions, the kidneys were perfused on RM3 organ perfusion machines (Waters Instruments, Inc.®, Rochester, MN), which provide a fixed-pressure system that allows adjustment to the perfusion pressure, as needed. All kidneys were perfused at a systolic pressure below 60mmHg. Perfusion characteristics (FL, RES, PT, [Na+], [C1-], [K+], [Ca++], and pH) were measured when the kidneys were placed on the machine perfusion system, every 30 minutes for the first 2 hours of MP, and every hour thereafter throughout the

period of MP. All chemical data were compared to a baseline assay of perfusate that had not circulated through the kidneys. All perfusion characteristics were standardized to 100 g of tissue weight.

Analysis

The following biochemical components of perfusate were measured every hour throughout MP with an Omni 4 Multianalyte system (Omni, AVL Medical Instruments, Atlanta, GA): [Na+], [C1-], [K+], [Ca++], and pH. All biochemical assays were standardized to 100g of tissue weight. For each measurement, a 0.5cc aliquot of perfusate is drawn from the perfusion chamber, analyzed by the Omni, and is available for evaluation within 30 seconds.

Statistical analysis

All data are reported as mean values ± SEM unless otherwise noted. Paired and unpaired student's t-tests were used where appropriate. All statistical analyses were performed by Statview 4.5 software (Abacus Concepts, Berkeley, CA).

EXAMPLE 1
Comparison of selected donor, preservation, and outcome variables by method and type of preservation (mean +/-SEM)
n = number of recipients
ns = not significant

Donor Characteristics	MPS (n=82) (Embodiment of Table 3)	Belzer-MPS (n=80)	p value (unpaired student's t-test)
Donor age (y)	62.8	64.2	ns
Final serum creatinine (mg/dl)	1.2	1.1	ns
Preservation characteristics			
Cold ischemic time (h)	28	27	ns
Outcome characteristics			
Delayed grant function (%)	11	21	0.03
1 yr. function (%)	95	95	ns

EXAMPLE 2
Comparison of selected donor, preservation, and outcome characteristics by method of machine perfusion solution (mean +/-SEM)
PGE1=prostaglandin E1(500mcg/L)
NTG=Nitroglycerin (5mg/L)

	PGE1 (n=152)	NTG (n=50)	PGE1+NTG (n=48) (Embodiment of Table 3)	Control-Belzer -MPS (n=140)	p value unpaired student's t-test)
Donor Characteristics					
Donor age (y)	41.1+/-6	44.3+/-5	42.2+/-9	44.1+/-5	0.72
Final serum creatinine (mg/dl)	1.0+/-0.2	1.2+/-0.3	0.9+/-02	0.8+/-0.5	0.45
Intraoperative urine output(ml)	240+/-80	220+/-90	300+/-100	240+/-60	0.56
Preservation characteristics					
Cold ischemic time (h)	24+/-4	23+/-4	22+/-6	23+/-4	0.61
Perfusion time (h)	17+/-3	19+/-6	15+/-8	16+/-5	0.33
Outcome characteristics					
Immediate function (%)	85+/-3	84+/-4	89+/-3	85+/-5	
Delayed grant function (%)	10+/-3	13+/-4	9+/-2	18+/-4	
3 month function (%)	95+/-4	93+/-2	96+/-3	87+/-5	

While the invention has been disclosed with reference to certain preferred embodiments, numerous modifications, alterations, and changes to the described embodiments are possible without departing from the sphere and scope of the invention, as defined in the appended claims and their equivalents thereof. For example, although the detailed description may refer, at times, to only organs, the terms "organs" and "organ" encompass all organs, tissues, and body parts that may be transplanted. Accordingly, it is intended that the invention not be limited to the described embodiments, but that it have the full scope defined by the language of the following claims.

What we claim is:

1. An organ or biological tissue preservation aqueous machine perfusion solution comprising:

a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties;

a nitric oxide donor; and

a glutathione-forming agent.

2. The machine perfusion solution of claim 1 wherein the prostaglandin comprises prostaglandin E1.

3. The machine perfusion solution of claim 1 wherein the prostaglandin has cellular and organelle membrane stabilization properties and cytoprotective properties.

4. The machine perfusion solution of claim 1 wherein the nitric oxide donor comprises nitroglycerin.

5. The machine perfusion solution of claim 1 wherein the glutathione-forming agent comprises N-acetylcysteine.

6. The machine perfusion solution of claim 1 further comprising KH_2PO_4, sodium gluconate, magnesium gluconate, adenine, and ribose.

7. The machine perfusion solution of claim 1 further comprising $CaCl_2$, HEPES, glucose, mannitol and pentastarch.

8. The machine perfusion solution of claim 1 further comprising NaCl and KOH.

9. The machine perfusion solution of claim 1 wherein the prostaglandin comprises about 100-10,000mcg/L prostaglandin E1, the nitric oxide donor comprises about 1-15mg/L nitroglycerin, and the glutathione-forming agent comprises about 0.1-5mg/L N-acetylcysteine, further comprising:

about 40-160mM sodium gluconate;

about 10-50mM KH_2PO_4;

about 1-15mM magnesium gluconate;

about 1-15mM adenine;

about 1-15mM ribose;

about 0.1-2mM $CaCl_2$;

1-30mM HEPES;

about 1-30mM glucose;

about 10-100mM mannitol; and

about 40-60g/L pentastarch.

10. The machine perfusion solution of claim 1 wherein the prostaglandin comprises about 250-2,500mcg/L prostaglandin E1, the nitric oxide donor comprises about 3-8mg/L nitroglycerin, and the glutathione-forming agent comprises about 0.5-2mg/L N-acetylcysteine, further comprising:

about 60-100mM sodium gluconate;

about 20-30mM KH_2PO_4;

about 3-8mM magnesium gluconate;

about 3-8mM adenine;

about 3-8mM ribose;

about 0.3-0.8mM $CaCl_2$;

about 8-15mM HEPES;

about 8-15mM glucose;

about 15-50mM mannitol; and

about 45-55g/L pentastarch.

11. The machine perfusion solution of claim 1 wherein the prostaglandin comprises about 500mcg/L protaglandin E1, the nitric oxide donor comprises about 5mg/L nitroglycerin, and the glutathione-forming agent comprises 1mg/L N-acetylcysteine, further comprising:

about 80mM sodium gluconate;

about 25mM KH_2PO_4;

about 5mM magnesium gluconate;

about 5mM adenine;

about 5mM ribose;

about 0.5mM $CaCl_2$;

about 10mM HEPES;

about 10mM glucose;

about 30mM mannitol; and

about 50g/L pentastarch.

12. The machine perfusion solution of claim 1 further comprising at least one of distilled water and deionized water.

13. A preserved organ or biological tissue comprising at least one of a cadaveric organ and tissue within the machine perfusion solution of claim 1 in at least one of a deep hypothermic condition and physiological condition.

14. The preserved organ or biological tissue of claim 13 wherein the machine perfusion solution is infused through vasculature of at least one of a cadaveric organ, living donor organ, and tissue.

15. The preserved organ or biological tissue of claim 13 wherein the machine perfusion solution is infused over or through a vascular biological substance to maintain viability of at least one of the cadaveric organ and tissue during an ex vivo period.

16. The preserved organ or biological tissue of claim 13 wherein the deep hypothermic condition comprises a temperature of about 2-10°C.

17. The preserved organ or biological tissue of claim 13 wherein the physiological condition comprises a temperature of about 37°C.

18. A perfusion machine comprising:

a chamber that mimics at least one of a deep hypothermic environment and physiological environment; and

the machine perfusion solution of claim 1 that continuously circulates through the chamber.

19. The perfusion machine of claim 18 further comprising:

a unit for static monitoring of at least one of an organ and tissue.

20. An organ or biological tissue preservation aqueous machine perfusion solution comprising:

about 100-10,000mcg/L prostaglandin E1;

about 1-15 mg/L nitroglycerin;

about 0.1-5 mg/L N-acetylcysteine;

about 40-160mM sodium gluconate;

about 10-50mM KH_2PO_4;

about 1-15mM magnesium gluconate;

about 1-15mM adenine;

about 1-15mM ribose;

about 0.1-2mM $CaCl_2$;

1-30mM HEPES;

about 1-30mM glucose;

about 10-100mM mannitol;

about 40-60g/L pentastarch; and

about 700-900mL sterile water.

21. A method for preserving an organ or biological tissue comprising:

pouring the machine perfusion solution into a chamber that mimics at least one of a deep hypothermic environment and physiological environment, the machine perfusion solution comprising a prostaglandin having vasodilatory, membrane stabilizing, platelet aggregation prevention upon reperfusion, and complement activation inhibitory properties, a nitric oxide donor, and a glutathione-forming agent;

circulating the machine perfusion solution continuously through the chamber;

inserting at least one of a cadaveric organ and tissue into the chamber; and

flushing the at least one of a cadaveric organ and tissue with the machine perfusion solution.

22. The method of claim 21 wherein the flushing comprises:

infusing the solution through vasculature of the at least one of a cadaveric organ and tissue.

23. The method of claim 21 wherein the flushing comprises:

infusing the solution over or through an avascular biological substance of the at least one of a cadaveric organ and tissue to maintain viability during an ex vivo period.

24. The method of claim 21 further comprising:

monitoring parameters of the at least one of a cadaveric organ and tissue.

25. The method of claim 21 further comprising:

exsanguinating the at least one of a cadaveric organ and tissue; and

replacing the machine perfusion solution with at least blood to return the at least one of a cadaveric organ and tissue to a normothermic condition.

26. A method of preparing an organ or biological tissue preservation machine perfusion solution comprising:

providing a solution with sterile water;

adding sodium gluconate, potassium phosphate, adenine, ribose, calcium chloride, pentastarch, magnesium gluconate, HEPES, glucose, mannitol, and insulin to the solution; and

mixing prostaglandin E1, nitroglycerin and N-acetylcysteine into the solution.

27. The method of claim 26 further comprising:

mixing the solution until all components are dissolved.

28. The method of claim 26 further comprising:

infusing the pentastarch under pressure through a dialyzing filter;

centrifuging the prostaglandin E1 under hypothermic conditions; and

filtering the centrifuged prostaglandin E1.