

# Limiting the Side Effects of Organ Preservation

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**Abstract** The possibility of preserving organs outside the body at two different temperatures, known as cold and normothermic organ preservation has strengthened the potential of expanding donor list and better predicting the outcome. Reactive oxygen species (ROS) production seems to be a very important player in regulating the level of damage in both methods of preservation. The main side effect of cold organ preservation which is known to lead to ischemia reperfusion injury, is highly dependent on ROS production. Thus, warm preservation has recently come to attention. This method is an expensive, sophisticated method which needs large volumes of blood for perfusion of the extracted organ and does not fully inhibit side effects of organ preservation. Thus, implementation of the currently used preservation solutions with established benefits such as UW, with recently found molecules such as hydrogen sulfide or substances which either directly or indirectly increase the levels of this substance by activating cellular pathways such as transsulfuration, could increasingly limit the still damaging properties of preservation. This further prevents delayed organ function or organ rejection due to low organ viability after preservation while increasing organ availability. This simple approach would expand the organ preservation time and help to enhance organ quality for more successful organ transplantation.

**Keywords:** *hypothermia damage, warm preservation, organ preservation solutions, hydrogen sulfide*

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## 1. Introduction

Organ preservation (OP) is the maintenance of the viability of an organ outside an organism. This is followed by restoration of normal function after being returned to an organism, a process known as transplantation [1]. Adequate preservation of organs intended for transplantation against cellular injury is critical to the proper functioning of the organ following transplantation. The recognition that organ preservation is an important factor in transplantation outcome has led to the development of many new static cold storage preservation solutions [2].

Although the hypothermic static storage of explanted solid organs in specialized cold crystalloid solutions still remains the best accepted preservation method for transplantation [3] recently warm preservation has come to attention. Both these method, though, still show specific setbacks and flaws. For example one of the main problems usually attributed to the cold organ preservation techniques that are used after the harvest of an organ is DGF or delayed graft function referring to the function of an organ that is impaired but eventually returns to normal. Warm preservation on the other hand has posed new challenges such as high lactate production. Both these shortcomings might lead to the specific changes in cellular physiology that could be responsible for a possible early organ rejection or failure.

This recognition has led to a renaissance in the study of organ preservation solutions and techniques. Preserving the organs for a longer period of time in preservation solutions, without increasing organ damage is the main goal set to minimize the sideeffects of transplantation. Thus better preservation solutions for longer storage are welcomed to further reduce incidence of primary or late graft dysfunction.

As current preservation solutions may have reached the limit of what is possible in terms of explant longevity and viability, the research attention has been turned to novel organoprotective pharmacotherapeutics that could provide the next generation of explant/transplant nurture [4]. New extracellular preservation solutions have contributed in decreasing the incidence of primary graft dysfunction over the last decade leaving more room to extend the donor criteria and ischemic time [5].

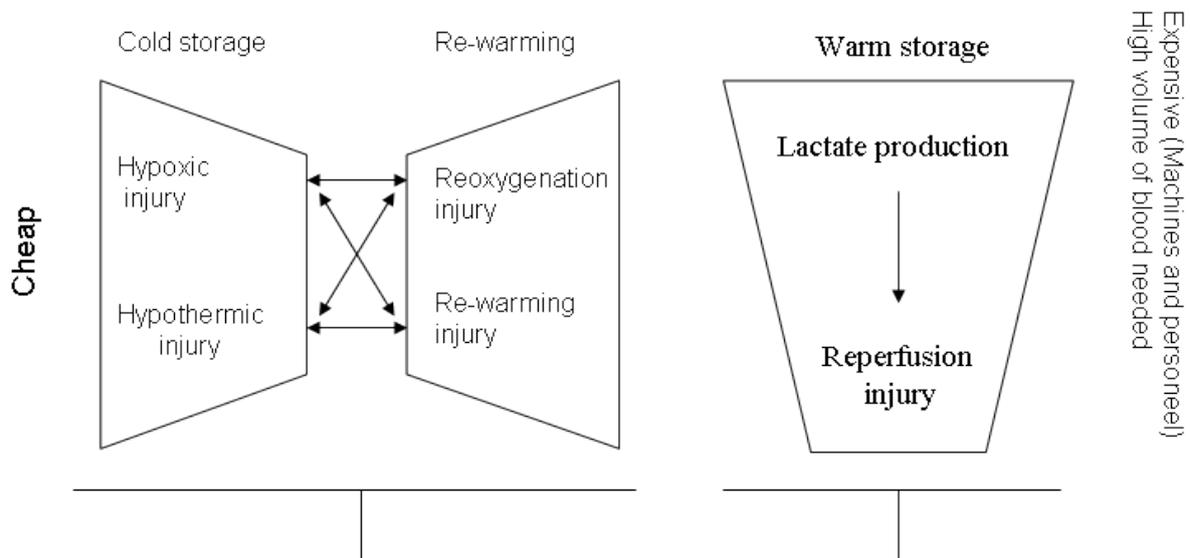
Enhancements in the quality of organ preservation and an extension of the viable preservation period, in particular, are keys to avoiding primary graft dysfunction or delayed function which ultimately expand the donor pool. These are the goals set forward to develop new organ preservation solutions. This review focuses on comparing different organ preservation induced injury types, to find overlapping obstacle and finally provide a number of non-immunological strategies to improve warm and cold preservation which afford cellular protection.

## 2. Cold and Normothermic Organ Preservation Sideeffects

A serious problem facing transplantation has been the preservation of an organ without significant damage or cell death to decrease rejection as part of the body's natural reaction to nonviable cells [6]. Even though normothermic and cold preservation are both currently available and seemingly successful methods in organ preservation, still the side effects of each method should be well studied and improvements during the preservation must be made to enhance the outcome of both methods. In this regard the impairment of the cellular homeostasis is probably a major obstacle in organ transplantation today. In a classic scheme of cold preservation, an organ will go through different phases such as pre-preservation, cold preservation, rewarming and reperfusion [7]. Mechanisms of cell injury during hypothermia induced hypoxia which have been partially characterized are mainly due to altered ion homeostasis, abnormalities in the mitochondrial respiratory chain and microsomal free iron release. Together these enhance the capacity for ROS generation on reoxygenation, a process known as reperfusion. ROS production increases F2-isoprostane formation, a potent vasoconstrictor product of lipid peroxidation and increases mitochondrial permeability leading to mitochondrial swelling and finally the release of pro-apoptotic factors into the cytoplasm which results in energy depletion, hypothermic necrosis, acidosis and finally cell death. Organs used for transplantation that undergo prolonged periods of cold ischemic preservation incur heavy damage from oxygen free radicals following reperfusion. In postischemic kidneys cold storage and reperfusion both cause loss of cell polarity, disruption of the cytoskeleton, and perturbations in the polarized membrane transport proteins [8].

Lowering the temperature causes a phase transition of lipids in membranous structures and results in profound changes in membrane stability. In addition, it drastically alters the function of membrane-bound enzymes. Compounding this injury are the deleterious events attendant on rewarming and reperfusion, which include ROS generation, activation of proteolytic enzymes, vascular endothelial injury and inflammation that can lead to allograft rejection [9]. In this regard two of the underlying mechanisms of the cold injury are the impairment of aerobic energy production by the mitochondria and cellular swelling which are both due to the impairment of Na/K ATPase enzyme leading to membrane water permeability. For example the accumulation of the lactate and free fatty acids inside the plasma in hypothermia preservation model also indicates a shift from aerobic metabolism to anaerobic [10].

Thus, cold storage as explained has different limitations even though the method is cheap and easy to use. Reperfusion from a metabolically inactive state results in endothelial cell injury, fluid and inflammatory cell accumulation. Thus another preservation method known as warm organ preservation has been introduced in hopes to limit cold preservation side effects such as DGF. In warm organ preservation the cold ischemia time (4-6 hours) decreases to less than an hour thus decreasing the chance of dysfunctional organs. Warm perfusion though seems to pose new challenges such as the large volume of patient blood to process the perfusion machine and the production of lactate and the monitoring which needs a greater number of personnel making this method very expensive [11].



**Figure 1.** A comparison between advantages and disadvantages present in warm and cold organ preservation

Regulating and maintaining the homeostasis becomes more important for organs such as liver in which pre-preservation (living and cadaver donors) has an impact on the sensitivity of the organ to damage. Brain death for example induces alterations in the donor liver to render it more sensitive to IR (ischemia reperfusion) injury and has an impact on the survival of transplanted organs [12]. In this case its most probable that the destruction of the cells occurs primarily via cell-mediated immune responses to IR induced cell damage [13].

### 3. Organ Preservation Solutions in Cold and Warm Preservation

Organ preservation is the supply line for organ transplantation [14]. Different strategies are incorporated to prevent damage to the solid organ and tissue. The solutions used for cold storage mimic either the intracellular or extracellular electrolyte milieu and are

formulated to protect against hypothermia-induced cell swelling, loss of membrane function, acidosis, cellular energy depletion and reactive oxygen species (ROS) formation. This method is based on the clearing of the blood from the tissue and the replacement with another fluid that prevents the damage in hypothermia. Various flush solutions are used for cold organ preservation with similar purposes: to prevent cellular edema, to delay cell death, and to maximize organ function after perfusion. Some of these solutions are; Euro-Collins solutions containing high concentrations of potassium, magnesium, phosphate, sulfate, and glucose. Ross-Marshall citrate solutions which in electrolytic composition is similar Euro-Collins except that citrate replaces phosphate, and mannitol replaces glucose stabilizer to stabilize the extracellular environment. Bretschneider histidine tryptophan ketoglutarate solution, Phosphate-buffered sucrose solution, Celsior solution, Kyoto ET solution and HTK solution are more recently made and used solutions in cold organ preservation. On the basis of the knowledge of the mechanisms of warm and cold ischemic and reperfusion injury to organs—University of Wisconsin (UW) Solution seems to be particularly useful in improving preservation of the liver and pancreas and it appears to be also superior to other organ preservatives because of its wide range of applicability in heart [15], lung [16], liver, kidney, pancreas, and bowel preservation. It's still not clear how UW solution could be more beneficial in protecting organs compared to other preservation solutions but it has been suggested that where most of the other preservatives are composed of buffered saccharide solutions (sucrose, glucose, mannitol, citrate, phosphate, sulfate, histidine) to prevent hypothermia induced cell swelling the UW solution uses an anion of relatively large molecular mass, lactobionate (MW = 358 kDa) to suppress the process, which is the key component making the difference [17]. Lactobionate is a relatively strong chelator of calcium, and iron [18] which might partially explain its efficacy in cold storage through a reduction in oxidative injury in cold-stored tissues. Replacing lactobionate with similar agents, such as gluconate, has not been as successful in organ preservation. Despite the benefit of UW solution for other organs (liver, pancreas), maximum storage times for intestine remain relatively brief (6- 10 h) and graft quality is often compromised. Thus other preservation solutions are being designed to help with the shortcomings of UW solution. For example AA solution containing different amino acids was designed and introduced for intestines preservation. This solution delivers a trophic stimulus, thereby facilitating energy production and control of oxidative stress [19].

Warm blood autoperfusion is used to prevent damage to organs in warm preservation. Organ preservation by warm perfusion, maintaining physiological pressure and flow parameters, has enabled prolonged preservation and successful transplantation of both normal livers and those with substantial ischemic damage lowering the ischemic damage. Lactic acid production is suggested to be the most important problem observed in this method, but ROS formation and its consequences might still be the underlying cause.

#### 4. A New Approach to Overcome Organ Preservation Side Effects

Organ preservation is the supply line for organ transplantation and thus of great importance. It is a further objective of this review to present a general guideline for implementation of organ preservation solutions considering all the different aspects of damage to an organ during the preservation process. Defects present in organ preservation methods, either cold or warm preservation, are a known fact which become more drastic considering that organ shortage is already one of the main limitations in organ transplantation. Seeking to maintain organ viability for transplantation [20] asks for improvement in the functionality of the present solutions which could further facilitate the success of the process and contribute immensely to the outcomes [21]. As ROS formation could be the main overlapping side effect of cold and warm preservation, it's well noted that different antioxidants are incorporated in preservation solution, but still the inhibition of ROS formation seems to not be strong enough and in one way or the other, organ damage is still observed. Further, amongst the defects encountered when organ preservation solutions are used are microcirculatory disturbances [22] and therefore, erythrocyte deformability should be prevented to maintain microcirculation to render the process of organ extraction, preservation and transplantation less injurious to the organ circulation. Also prevention of organ infection during the process of preservation and transplantation is of utmost importance. For example intestinal poor organ viability after transplantation is usually due to bacterial infections leading to the loss of barrier function and bacterial translocation accompanied by life-threatening inflammatory infections. Thus it becomes very important to consider all the different aspects of organ preservation before formulating or choosing a solution to preserve a specific organ. According to the above a reliable approach would be the prevention of organ damage (DGF) by stronger preventive measures for example by inducing the production of intracellular protective factors such as NO or H<sub>2</sub>S (hydrogen sulfide) against ROS damage while helping to strengthen cell membrane pores, and membrane function to prevent water permeability, cell swelling and organ infection.

The principles of organ preservation suggest that maintenance of cellular viability is of utmost importance to proper organ function following transplantation. In that regard, the organ preservation or maintenance solution contains a macromolecule in a colloid form to prevent cellular swelling and rupture during the preservation and recovery periods. D-glucose, fructose and magnesium ions are able to support the anaerobic metabolism of glucose during hypothermia preservation or the aerobic metabolism during warm preservation to produce adequate amounts of adenosine triphosphate (ATP). A preferred embodiment also contains antioxidants or reducing agents, since following transplantation, highly toxic oxygen radicals are known to be formed, and the addition of such agents help serve to mute the lethal effects of these radicals during the vulnerable period after transplantation.

Acidosis is one of the side effects of both cold and warm preservation which causes cellular injury due

mainly to the quick normalization of pH value after transplantation. Preventing the acidic intracellular environment during preservation might show to be a protective factor in both methods. Further, DNA damage occurs during organ preservation and therefore reducing oxidative DNA damage could be beneficial to organ preservation [13]. Recently gene transfer of numerous cytoprotective and immunomodulatory molecules has yielded very promising experimental results. Some of the cytoprotective molecules genetically transferred to explanted organs include heme oxygenase I, endothelial nitric oxide synthase, superoxide dismutase, and antisense oligodeoxynucleotides specific for transcription factor NF-1d3 or ICAM\_1. More recently we have found that co-transfection of VMAT-1 (vesicular monoamine transferase) and TPH-1 (tryptophan hydroxylase) in rat aortic smooth muscle cells and kidney tissue creates a serotonin-vesicular phenotype which protects cells against hypothermia damage [23]. Another strategy to limit injury may involve the technique of preconditioning. Single or repeated periods of ischemia can provide a protective effect against subsequent prolonged episodes of ischemia [4]. This is probably accomplished by upregulation of certain proteins and genes which help to protect organs through longer periods of preservation.

Proteinases are another major obstacle in organ preservation and proteinase inhibitor supplementation as an extracellular matrix stabilizer improves graft function. Other substances such as glutathione and nitric oxide (NO) donors have shown beneficial effect on vascular function and endothelial cell survival, in the face of oxidative stress. Treating the organs by the other gas mediators such as CO [24] or H<sub>2</sub>S [25] has also shown cell preservative effects. Certain pharmacologically active substances such as dopamine has have been shown previously to protect from hypothermia induced apoptosis in cultured cells [26,27] and to improve graft patency in human kidney transplantation [28].

From the above, it seems plausible that only the use of one or two substances with high potential in protecting against cellular damage, could provide all the qualities mentioned in a preferred organ preservation medium while presenting a new outstanding platform for development of super sustainable mediums with maximum cellular protection. Specially, if such substances would also be present in animals and provide a protective mechanism against cellular damage in nature, they would be better accepted by the medical society. During our recent studies we have shown that hibernating hamsters have adopted specific methods to withstand damage during torpor and the following reperfusion. Examples of such mechanisms are tissue remodeling [29] and suppression of immune system [30]. Mammalian hibernation consists of a series of torpor bouts interspersed by brief periods of arousal. During torpor the animals enter a state of 'hypometabolism' in which many energy consuming processes are lowered to levels significantly below those of euthermic animals. During hibernation organs enter a hypothermic condition/torpor, after which blood flow is reduced while body temperature rises to normal levels/arousal. Thus, the arousal period in hibernation is associated with organ reperfusion at increasing body temperatures and restored organ functionality. The data have shown that hibernating

animals can fully preserve organ structure under extreme conditions such as severe ischemia, hypothermia and reperfusion which are all also observed in cold organ preservation and later transplantation. Elucidation of the mechanisms involved in such a natural model of organ preservation could be relevant to human medicine in general specially in organ preservation [31]. In our studies on hamster cells we identified that certain substances such as serotonin and dopamine [23,32] protect cells through activation and upregulation of CBS (cystathionine beta synthase) an enzyme which produces H<sub>2</sub>S. Further we have shown that also NaHS, which releases H<sub>2</sub>S, protects cells against damage upon cell cooling and rewarming [32]. The mechanism by which H<sub>2</sub>S attenuates apoptosis is unknown, but has already been suggested to constitute of compensation for the loss of SH-reduction equivalents during cold preservation [26], or alternative mechanisms such as suppression of ROS formation or induction of a protective type of autophagy [33,34,35] could be responsible for protection from hypoxic injury in cells, tissues and animals. On the molecular level, various signal transduction pathways downstream of H<sub>2</sub>S have been implicated (reviewed in [36]), including the opening of ATP-sensitive K<sup>+</sup> channels, activation of eNOS and the activation of pro-survival kinases ERK, PKC isoforms and PI3K-Akt, resulting in augmented expression of heat shock proteins, Bcl-2 and Bcl-xL. On the other hand we have found that intracellular production of H<sub>2</sub>S might prevent organ remodeling [37] and potentially be of use in prevention of pathogenic organ remodeling leading to organ dysfunction known to occur after transplantation [38,39].

## 5. Opinions and Discussion

Each day a percentage of patients on the waiting list of transplantation receive an organ transplant but another percentage lose their lives on the waiting list, either due to the absence of available organs or early and late graft rejection. The timing after organ harvesting and transplantation in which the organ has to be placed and kept in organ preservation solution either in warm or cold preservation is important to organ performance. For example long graft cold ischemia time is associated with increased arterial stiffness in transplant recipients. Cold preservation has different side effects which were discussed in this review, mainly due to hypothermia induced ischemia reperfusion. Warm organ preservation was introduced to cover for this side effect. But although this technique was shown to be able to limit the side effect associated to cold preservation, the high costs and the high volume of blood needed for the process and finally the production of lactate still limited its usefulness. Finding a way to limit the side effect of cold organ preservation would seem a more reasonable approach in organ preservation. The addition of certain substances such as dopamine and serotonin seem to protect cells and tissues against damage, keeping the donor organ in an optimal morphological and viable state [40].

University of Wisconsin (UW) solution has revolutionized cold ischemic preservation of solid organs, permitting safe preservation times of up to 72 hours. It now remains the most widely utilized solution for cold

preservation of intra-abdominal organs. The composition of UW solution has been designed to counter the theoretical problems associated with cold ischemic preservation, namely to minimize hypothermic-induced cell swelling, prevent intracellular acidosis, prevent expansion of interstitial space, prevent oxygen free radical induced injury, and finally to prevent cold-induced cell death. There has been little change to the components of UW solution since its conception, but in vitro and in vivo studies have shown that many of the components of UW solution confer little benefit. These studies have suggested that it is possible to improve upon UW solution by simplification and the elimination of several components; only lactobionate, raffinose and glutathione have been considered as truly essential [41]. Although this method of organ preservation is effective, some organs (5–15%) of livers and 20–30% of kidneys do not function well upon transplant [2]. Although intra-abdominal organs are well preserved at present, intra-thoracic organs (lungs and heart) are less well preserved, and better methods for preservation of these organs are needed for increased use of lung and heart transplantation. As mentioned in this review, still no perfect preservation medium has been formulated to prevent all side effects of organ preservation for transplantation. Therefore, it's important to keep in mind that the main side effect behind cold and warm preservation still remains the production of ROS and thus any future research should focus on the possibility of the prevention of ROS formation and cellular damage, to reach the final goal of long term organ survival outside the body without preservation side-effects. Thus, it would seem reasonable to implement the already well known mediums such as UW with substances that upregulate the intracellular production or presence of certain antioxidants such as H<sub>2</sub>S, which would increase the full potential of organ preservation with little need for incorporating expensive techniques.

## References

- [1] Lillehei RC, Manax WG, Bloch JH, Eyal Z, Hidalgo F, Longerbeam JK: In vitro preservation of whole organs by hypothermia and hyperbaric oxygenation. *Cryobiology*. 1:181-193, 1964.
- [2] Maathuis MH, Leuvenink HG, Ploeg RJ: Perspectives in organ preservation. *Transplantation*. 83:1289-1298, 2007.
- [3] Moers C, Leuvenink HG, Ploeg RJ: Donation after cardiac death: Evaluation of revisiting an important donor source. *Nephrol Dial Transplant*. 25:666-673, 2010.
- [4] Laight DW: Therapeutic approaches to organ preservation injury. *Expert Opinion on Therapeutic Patents*. 15:1489-1496(8), 1 November 2005.
- [5] Van Raemdonck D: Thoracic organs: Current preservation technology and future prospects; part I: Lung. *Curr Opin Organ Transplant*. 15:150-155, 2010.
- [6] Dyer P, Johnson R: The historical basis of current challenges in organ transplantation. *Surgery (Oxford)*. 22:312-318, 2004.
- [7] Jeevanandam V: Improving donor organ function-cold to warm preservation. *World J Surg*. 34:628-631, 2010.
- [8] Shoskes DA, Halloran PF: Delayed graft function in renal transplantation: Etiology, management and long-term significance. *J Urol*. 155:1831-1840, 1996.
- [9] Strom TB, Suthanthiran M: Therapeutic approach to organ transplantation. *Nephrology Dialysis Transplantation*. 11:1176-1181, 1996.
- [10] Boutilier RG: Mechanisms of cell survival in hypoxia and hyperthermia. *J Exp Biol*. 204:3171-3181, 2001.
- [11] Jeevanandam V: Improving donor organ function-cold to warm preservation. *World J Surg*. 34:628-631, 2010.
- [12] Broelsch CE, Frilling A, Testa G, Cicinnati V, Nadalin S, Paul A, Malago M: Early and late complications in the recipient of an adult living donor liver. *Liver Transpl*. 9:S50-3, 2003.
- [13] Fitton TP, Barreiro CJ, Bonde PN, Wei C, Gage F, Rodriguez R, Conte JV: Attenuation of DNA damage in canine hearts preserved by continuous hypothermic perfusion. *Ann Thorac Surg*. 80:1812-1820, 2005.
- [14] Southard JH, Belzer FO: Organ preservation. *Annu Rev Med*. 46:235-247, 1995.
- [15] Swanson DK, Pasaoglu I, Berkoff HA, Southard JA, Hegge JO: Improved heart preservation with UW preservation solution. *J Heart Transplant*. 7:456-467, 1988.
- [16] Xiong L, Mazmanian M, Chapelier AR, Reignier J, Weiss M, Darteville PG, Herve P: Lung preservation with euro-collins, university of wisconsin, wallwork, and low-potassium-dextran solution. universite++ paris-sud lung transplant group. *Ann Thorac Surg*. 58:845-850, 1994.
- [17] Sumimoto R, Kamada N: Lactobionate as the most important component in UW solution for liver preservation. *Transplant Proc*. 22:2198-2199, 1990.
- [18] Den Butter G, Saunder A, Marsh DC, Belzer FO, Southard JH: Comparison of solutions for preservation of the rabbit liver as tested by isolated perfusion. *Transpl Int*. 8:466-471, 1995.
- [19] Fujimoto Y, Olson DW, Madsen KL, Zeng J, Jewell LD, Kneteman NM, Bigam DL, Churchill TA: Defining the role of a tailored luminal solution for small bowel preservation. *Am J Transplant*. 2:229-236, 2002.
- [20] Mühlbacher F, Langer F, Mittermayer C: Preservation solutions for transplantation. *Transplant Proc*. 31:2069-2070, 1999.
- [21] Brockmann J, Reddy S, Coussios C, Pigott D, Guirriero D, Hughes D, Morovat A, Roy D, Winter L, Friend PJ: Normothermic perfusion: A new paradigm for organ preservation. *Ann Surg*. 250:1-6, 2009.
- [22] Seifalian AM, Mallet SV, Rolles K, Davidson BR: Hepatic microcirculation during human orthotopic liver transplantation. *Br J Surg*. 84:1391-1395, 1997.
- [23] Talaei F, Schmidt M, Henning RH: Induction of VMAT-1 and TPH-1 expression induces vesicular accumulation of serotonin and protects cells and tissue from Cooling/Rewarming injury. *PLoS One*. 7:e30400, 2012.
- [24] Kohmoto J, Nakao A, Sugimoto R, Wang Y, Zhan J, Ueda H, McCurry KR: Carbon monoxide-saturated preservation solution protects lung grafts from ischemia-reperfusion injury. *J Thorac Cardiovasc Surg*. 136:1067-1075, 2008.
- [25] Hu X, Li T, Bi S, Jin Z, Zhou G, Bai C, Li L, Cui Q, Liu W: Possible role of hydrogen sulfide on the preservation of donor rat hearts. *Transplant Proc*. 39:3024-3029, 2007.
- [26] Brinkkoetter PT, Song H, Losel R, Schnetzke U, Gottmann U, Feng Y, Hanusch C, Beck GC, Schnuelle P, Wehling M, van der Woude FJ, Yard BA: Hypothermic injury: The mitochondrial calcium, ATP and ROS love-hate triangle out of balance. *Cell Physiol Biochem*. 22:195-204, 2008.
- [27] Yard B, Beck G, Schnuelle P, Braun C, Schaub M, Bechtler M, Gottmann U, Xiao Y, Breedijk A, Wandschneider S, Losel R, Sponer G, Wehling M, van der Woude FJ: Prevention of cold-preservation injury of cultured endothelial cells by catecholamines and related compounds. *Am J Transplant*. 4:22-30, 2004.
- [28] Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, Fischereder M, Jauch KW, Heemann U, Zeier M, Hugo C, Pisarski P, Kramer BK, Lopau K, Rahmel A, Benck U, Birk R, Yard BA: Effects of donor pretreatment with dopamine on graft function after kidney transplantation: A randomized controlled trial. *JAMA*. 302:1067-1075, 2009.
- [29] Talaei F, Hylkema MN, Bouma HR, Boerema AS, Srijckstra AM, Henning RH, Schmidt M: Reversible remodeling of lung tissue during hibernation in the syrian hamster. *J Exp Biol*. 214:1276-1282, 2011.
- [30] Bouma HR, Kroese FGM, Kok JW, Talaei F, Boerema AS, Herwig A, Draghiciu O, van Buiten A, Epema AH, van Dam A, Srijckstra AM, Henning RH: Low body temperature governs the decline of circulating lymphocytes during hibernation through sphingosine-1-phosphate. *Proceedings of the National Academy of Sciences*. 108:2052-2057, 2011.
- [31] Zancanaro C, Malatesta M, Mannello F, Vogel P, Fakan S: The kidney during hibernation and arousal from hibernation. A natural

- model of organ preservation during cold ischaemia and reperfusion. *Nephrol Dial Transplant*. 14:1982-1990, 1999.
- [32] Talaei F, Bouma HR, Van der Graaf AC, Strijkstra AM, Schmidt M, Henning RH: Serotonin and dopamine protect from Hypothermia/Rewarming damage through the CBS/ H<sub>2</sub>S pathway. *PLoS One*. 6:e22568, 2011.
- [33] Tang G, Wu L, Liang W, Wang R: Direct stimulation of K(ATP) channels by exogenous and endogenous hydrogen sulfide in vascular smooth muscle cells. *Mol Pharmacol*. 68:1757-1764, 2005.
- [34] Mustafa AK, Gadalla MM, Sen N, Kim S, Mu W, Gazi SK, Barrow RK, Yang G, Wang R, Snyder SH: H<sub>2</sub>S signals through protein S-sulfhydration. *Sci.Signal*. 2:ra72, 2009.
- [35] Talaei F: Modulation of endogenous H<sub>2</sub>S production: Its role in hibernation and pharmacological cell protection. S.l., 2011.
- [36] Calvert JW, Coetzee WA, Lefer DJ: Novel insights into hydrogen sulfide-mediated cytoprotection. *Antioxid Redox Signal*. 12:1203-1217, 2010.
- [37] Talaei F, Bouma HR, Hylkema MN, Strijkstra AM, Boerema AS, Schmidt M, Henning RH: The role of endogenous H<sub>2</sub>S formation in reversible remodeling of lung tissue during hibernation in the syrian hamster. *J Exp Biol*. 215:2912-2919, 2012.
- [38] Ramirez AM, Nunley DR, Rojas M, Roman J: Activation of tissue remodeling precedes obliterative bronchiolitis in lung transplant recipients. *Biomark Insights*. 3:351-359, 2008.
- [39] Rienstra H, Katta K, Celie JW, van Goor H, Navis G, van den Born J, Hillebrands JL: Differential expression of proteoglycans in tissue remodeling and lymphangiogenesis after experimental renal transplantation in rats. *PLoS One*. 5:e9095, 2010.
- [40] Talaei F, Bouma H, Van der Graaf A, Strijkstra A, Schmidt M, Henning R: Serotonin and dopamine protect from Hypothermia/Rewarming damage through the CBS/ H<sub>2</sub>S pathway. *PLoS ONE*. 6:e22568, 2011.
- [41] Tambyraja AL, Mitchell R, Driscoll PJ, Deans C, Parks RW, Rahman I, Megson IL: Glutathione supplementation to university of wisconsin solution causes endothelial dysfunction. *Transpl Immunol*. 18:146-150, 2007.