Brain dead donor graft deterioration and attenuation with N-octanoyl dopamine preconditioning

Hottenrott, Christina Maximilia Valentina

I

R1
R2
R3
R4
R5
R6
R7
R8
R9
R10
R11
R12
R13
R14
R15
R16
R17
R18
R19
R20
R21
R22
R23
R24
R25
R26
R27
R28
R29
R30
R31
R32
R33
R34
R35
R36
R37
R38
R39

Transplantation

In the second half of the last century the first successful kidney transplantation was performed [1]. It took more than two decades before the first successful lung transplantation followed, only enabled by the introduction of adequate immunosuppression [2]. With the introduction of immunosuppression and advances in the operation technique first year graft survival tremendously improved by preventing acute rejection. Thereafter transplantation quickly became the treatment of choice for patients with chronic diseases [3, 4]. Unfortunately, the success in short term survival was expected to also influence the long-term graft survival, but the effect was little to none, as illustrated in figure 1 for kidney graft survival [5-7].

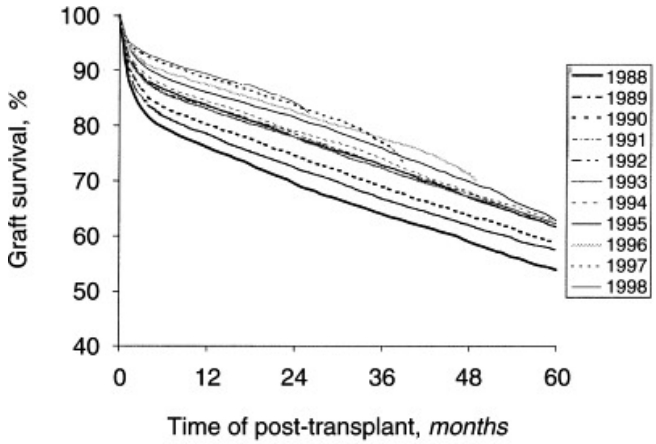

Figure 1. Long term graft survival has not improved after the introduction of immunosuppression. Superior graft survival over a decade are the result of an improved early 6 month's outcome after transplantation. After this period no differences are found in the trend of long-term graft survival, represented by the parallel progression of the survival curves in kidney transplantation [7].

Important for the understanding of the unchanged long-term graft survival in organ transplantation was the finding that even though kidneys procured from brain dead donors were better cross-matched, the outcome was inferior compared to transplantations using organs from living donors [8]. The main difference between these donors is cerebral insult leading to brain death with subsequent organ deterioration, and furthermore extended cold ischemia time [8-11]. However, also brain death and transplantation associated factors such as the need for ventilation [12, 13], inadequate hemodynamic stabilization [14] or hormonal resuscitation [15] contribute to the inflammatory response and subsequent reduction of organ function. The decrease in organ function, after the onset of brain death and cold ischemia/

reperfusion, have been associated with an increased risk for primary graft dysfunction (PGD) in the recipient [16-18]. PGD is yet another independent risk factor for chronic rejection and poor survival [19]. Therefore lung donors, with substantially impaired lung function, determined by the ratio of partial arterial oxygen pressure and fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, are not considered eligible for lung transplantation [20]. Also, in case of other transplantable organs, organ function prior to donation is a reason to refuse these organs. For example kidneys from donors with increased creatinine levels are declined for kidney transplantation [21]. Interestingly, the risk for PGD between organs of one multiorgan donor strongly correlates [17]. This suggests that strict donor management protocols are beneficial for all grafts if implemented as early as possible.

Brain injury and initiation of graft deterioration

With the rare exception of living lung lobe donors, lung grafts are almost exclusively derived from donors with some sort of brain injury. The majority are donors sustaining brain death. But even in case of donors after circulatory death (DCD; Table 1), brain injury is present. For instance, in DCD category 3, ventilation is switched off in patients with infaust neurologic prognosis. Also in DCD category 2 where resuscitation failed, the brain suffers from ischemia [22].

Table 1. Different donor categories after circulatory death, adapted from Detry et al. [22]

Categories	Description	Status
Category 1	Dead on arrival	Uncontrolled
Category 2	Unsuccessful resuscitation	Uncontrolled
Category 3	Cardiac arrest after switch off procedure	Controlled
Category 4	Cardiac arrest while brain dead (un-/expected)	Un-/ Controlled
Category 5	Medically assisted cardiocirculatory death (in hospital)	Controlled

Brain injury causes the release of cytokines and pro-inflammatory subcellular fragments into the blood stream [23, 24]. This initiates a systemic immune response with increased neutrophil activation and migration into the parenchyma [25]. Neutrophil granulocyte accumulation, their release of cytokines and oxidative burst contribute to parenchyma injury and development of acute respiratory distress syndrome (ARDS) [26]. ARDS is found in 15-20% of the brain injured patients [27]. Interestingly, the rate of acute kidney failure is comparable to the occurrence of ARDS in brain injury [28-30], suggesting a common denominator or cross-talk between the two organ systems.

Additionally, many brain injured potential organ donors develop neurogenic pulmonary edema (NPE) [31-33], enhanced by inflammation [34] and loss of epithelial integrity [35]. At the occurrence of NPE high ventilation pressures are needed to ventilate the lung and ensure oxygenation of the other organs. The high pressure ventilation results in enhanced lung injury [36], with a further increase in cytokines. Enhanced local cytokine release may cause a spill over into the circulatory system affecting distant organs [37], in particular the kidney [38].

Brain death and amplification of graft injury

Extensive brain injury may lead to brain death. As a result of venous engorgement and brain swelling the intracranial pressure increases to values above systemic pressure. Subsequently, the brain stem is forced towards the scull opening, the foramen magnum. This causes as a consequence of arterial compression tissue ischemia and infarction [39]. The injury leads to brain swelling and increase of intracranial pressure until intracranial circulation ceases [40]. The culmination of progressive rostral-to-caudal ischemia leads to brain death [41]. As a consequence of brain death four substantial pathophysiological changes are initiated i.e. (1) hemodynamic, (2) endocrinologic, (3) metabolic and (4) immunologic.

(1) The rostral-to-caudal ischemia at onset of brain death [41] is characterized by a typical sequence of hemodynamic changes, though they may vary between the individual donors and depend on the cause of brain death [42].

At first the pons becomes ischemic, causing the 'Cushing response', characterized as bradycardia and hypertension. This is followed by massive hypertension and tachycardia, as a result of 'catecholamine storm' upon ischemia of the medulla oblongata [40]. During this 'catecholamine storm' a massive increase of catecholamines in the blood occurs and is accompanied by a significant increase in systemic vascular resistance (SVR) [39, 43-45]. During this hyperdynamic phase arrhythmias occur [42], with increase in cardiac enzymes and ventricular dysfunction [46-49] influencing the post-transplantation phase after cardiac transplantation [42, 47].

The sudden increase in systemic vascular resistance with the short sudden hypertensive period is associated with rupture of the capillary-alveolar membrane [50]. As a result of cessation of the aortic blood flow and slight increase of the central venous pressure (CVP), a large proportion of the total blood volume is pooled in the cardio pulmonary vasculature [51]. The increased hydrostatic pressure causes pulmonary edema [52] and explains commonly found focal areas of erythrocytes in the pulmonary parenchyma [51].

I

Finally, total sympathetic denervation occurs [40, 53], resulting in hypotension and cardiac dysfunction [42, 51]. This autonomic dysregulation causes insufficient perfusion and oxygen delivery to the peripheral organs [54-56]. Supportive fluid loading and catecholamines are applied to prevent ischemia and organ injury. However, these mainly kidney protective measures can particularly harm the lung [14, 57-60].

(2) + (3) Endocrinologic and metabolic changes are evident in brain death but an in depth discussion is beyond the scope of this thesis. Briefly, after the onset of brain death circulating hormones - triiodthyronin, cortisol and insulin as well as antidiuretic hormone (ADH) are significantly reduced [39, 61-63]. This hypothalamic-pituitary dysfunction is the consequence of altered brain perfusion in individual donors after the onset of brain death, with different extent [64-68]. This endocrinologic dysregulation is associated with perfusion perturbation, mismatch of demand and oxygen supply ultimately accompanied by a shift from aerobic to anaerobic metabolism [55, 66, 69]. In the anaerobic state ATP is depleted. This depletion of ATP results in loss of barrier function, intensifying tissue injury [70].

Both, decreasing insulin levels and subsequently reduced cellular glucose uptake, as well as reduced metabolism arising from lack of thyroid hormones, eventuate in hypothermia [44, 71]. Additionally, the induced pro-inflammatory changes contribute to the dysbalance of thyroid hormones [72]. Evidence in other disorders of thyroid dysbalance suggest that the hormones are involved in regulation of systemic vascular resistance. Therefore, a fall of thyroid hormones could quickly lead to increased systemic vascular resistance, enhancing ischemia, and possibly intensifying brain death induced cardiac impairment [73] and ensuing endorgan injury.

(4) The inflammatory immune response initiated by the cerebral insult is exaggerated by the hemodynamic, endocrinologic and metabolic changes [74]. But even without previous cerebral injury, blood of brain dead animals administered to healthy animals induces an immune response, with deterioration of the peripheral organs [75]. This suggests that there is a release of potent, pro-inflammatory molecules into the blood upon brain death induced injury. The latest findings suggest damage associated molecular pattern (DAMP) molecules [24], or even more potent mitochondrial DAMPs (mtDAMPs) [76], released during sudden or extensive tissue injury [77], contributing to severe lung parenchyma injury [78]. Recently, it has been shown that upon stimulation with mtDAMPs the DAMP high-mobility group box-1 (HMGB1) is expressed [79]. In lung transplantation the systemic level of HMGB1 is one of the DAMPs associated with lung dysfunction before and after transplantation [80]. It is predictive for transplantation outcome [81]. Comparing living and deceased kidney

donor transplantation HMGB1 was only found in kidney parenchyma of deceased donors [82].
Related to the systemic release of mtDAMPs and HMGB1 neutrophil granulocytes are recruited. But also brain death induced shear stress and subsequent chemokines and adhesion molecules expression on the endothelial cells lead to migration of neutrophil granulocytes [83-85]. The extent of chemokine IL-8 release correlates with the number of migrated neutrophil granulocyte into the donor lung [86] predicting the impairment of graft function, development of early graft dysfunction and early mortality in the recipient after transplantation [86].
The combination of endothelial activation, subcellular fragment release and hemodynamic induced microcirculatory changes also exaggerate hemostasis [34, 77, 84, 87]. Hemostasis is initiated after the cerebral insult by release of pro-inflammatory cytokines and passage of blood through the injured cerebral tissue [88]. Clot formation occurs as a consequence of a dysbalance between an activated coagulation system and dysfunctional fibrinolysis in brain dead patients [89]. This may explain the relatively high incidences of pulmonary embolism (PE) in brain dead donors, with a respective risk of PGD for the recipient of the lung after transplantation [90]. The removal of these emboli reduces the risk for PGD in the lung recipient [91]. However many PE remain undetected in the donor [90].
All in all, the inflammatory response induced in the brain dead donor determines the success of transplantation [11, 92]. Thus, until alternative sources for organ transplants are found, it is of utmost importance to elucidate and target deleterious processes in brain death. Furthermore, lungs should carefully be selected for transplantation.

Cold ischemia and reperfusion

For allocation of lungs and other solid organ systems grafts are cold preserved at approximately 4 °C in order to reduce their metabolic rate and subsequently decrease their energy requirements [93]. Ironically, this protective measurement remains a significant, allogen-independent [9] cause of early morbidity and mortality in any solid organ transplantation [94], particularly after lung transplantation [18]. In approximately 20% of the lung recipients it leads to primary graft dysfunction [95], with a 30 day mortality of 50% [96]. The clinical and histological picture of primary graft dysfunction is comparable to ARDS and is associated with an increased risk of acute and chronic rejection [18, 97].

I

Cold ischemia leads to ATP depletion and reactive oxygen species (ROS) accumulation. The failure of the sodium-potassium ATPase with subsequent intracellular sodium accumulation leads to cell swelling and cytosolic calcium arises [98-105]. Along with the activation of mitochondrial transition pores and the release of free iron molecules cell death is induced [106-108]. The lack of oxygen forces cells to switch from aerobic to anaerobic metabolism, resulting in acidosis [100]. These changes are deleterious but may be limited using adequate preservation solutions and limiting cold ischemic time. In the lung this can be achieved using a low-potassium dextrane solution and inflating the lungs with oxygen which both guard and preserve cell integrity [18]. However ischemia induced injury may be exaggerated by reperfusion resulting in necroptosis, which has been associated with the release of damage associated molecular patterns (DAMPs) provoking a strong inflammatory immune response [109].

The first minutes after reperfusion are considered to be crucial for the extent of reperfusion injury [110, 111], partially as result of increased endothelial permeability [110, 112] and because of the previously induced changes. It led to the development of controlled reperfusion strategies. This concept of controlled reperfusion pressure resulted in substantial attenuation of lung injury, even clinically [113-115]. However controlled reperfusion is commonly combined with leukocyte depletion, because leukocytes are considered to be the key players in progression of lung reperfusion injury [116, 117]. Leukocytes are believed to be the major source of oxidative stress and origin of cellular injury [118]. This injury seems to consist of two different phases, an earlier macrophage transmitted injury and a later neutrophil granulocyte transmitted injury [119-121]. Passenger macrophages [121] and DAMPs [80, 122, 123] initiate the pro-inflammatory response to reperfusion [120]. In combination with the activation of the endothelium [124, 125], it leads to migration of host neutrophil granulocytes- the second phase of ischemia reperfusion injury [126]. However de Perrot et al. [127] have convincingly shown that, independent of neutrophil granulocytes, also the host T lymphocytes strongly contribute to the second phase of ischemia reperfusion injury.

The initial insult by brain death is considered to increase susceptibility to the second insult i.e. ischemia reperfusion injury [128], however both are inevitable in the current transplantation process. The limitation or prevention of inflammation should have priority in protocols for reperfusion since the immune cell activation leads to the release of pro-inflammatory molecules [129] and oxidative stress [18] with systemic impact [130]. Ventilation strategies might be part of such a protocol [96].

Ventilation: Pre- and post-transplantation phase

As mentioned before, both during brain death and ischemia reperfusion, acute lung injury arises [131, 132]. This injury is on a histological level characterized by infiltration of neutrophil granulocytes, protein rich intra-alveolar exudate and alveolar-capillary disruption [86, 132], resulting in the deterioration of lung function and increasing airway resistance [133].
Until the mid 80ies, in case of acute lung injury, lungs were ventilated with high tidal volumes or high pressure favoring better pH and reduced $PaCO_2$, considering a homogenously stiff lung. However, with the introduction of computer tomography in the clinic in the mid 80ies, it became obvious that acute respiratory distress syndrome effects lung parenchyma in-homogenously [134]. Around the same time it became evident that application of high pressure, independent of pre-existing injury, severely impairs lung parenchyma with subsequent loss of function [36]. The first study comparing high tidal volume (traditional approach) to low tidal volume (new approach) ventilation clearly showed that mortality, days on the ventilator and needed inspiratory pressure were significantly reduced under the new approach [135]. Importantly, with the shortage of eligible lung donors for transplantation the change from traditional ventilation to lung protective ventilation strategy resulted in a significantly higher rate of lung transplants suitable for transplantation [12]. In the short term, 6 month survival was not different between the ventilation strategies [12]. De Perrot et al. [13] showed that during the early phase of ischemia reperfusion injury conventional mechanical ventilation impairs the lung function and exacerbates the immune response compared to protective lung ventilation. This finding is particularly important since the majority of recipients requires mechanical ventilator support for the first few hours after transplantation. The pronounced immune reaction may impair other organs [38] and might explain increased morbidity and mortality in patients with primary graft dysfunction [129].

Preconditioning

At any time point in the transplantation process, graft quality determines the fate of transplantation. Takada et al. [75] were one of the first describing that graft quality is impaired in peripheral organs after onset of brain death. The pro-inflammatory immune response induced by brain death is considered to be the origin of the inferior outcome after transplantation compared to living organ donation [8]. For that reason the limitation of the inflammatory response and maintenance of organ

I

quality in brain dead donors has become the focus of intensive research. In particular, while before the typical donor was a healthy young donor with acute traumatic injury leading to brain death [136], today the typical donor is an old donor with spontaneous cerebral hemorrhage and preexisting comorbidities [137, 138] with an increased risk for primary graft dysfunction [139-141]. This is possibly the result of the pro-inflammatory nature of the comorbidities [142].

One important consideration for prevention of organ deterioration is to stabilize brain dead donors close to physiological values [136]. For that reason strict donor management protocols were implemented to stabilize donors adequately, which increased the number of organs suitable for transplantation tremendously [15]. Part of these protocols is sometimes hormonal resuscitation treatment, reversing the brain death induced endocrinologic changes. This resulted in superior hemodynamics and aerobic metabolism in the donor [69, 143, 144], and improved outcome in the recipient [145]. Conversely, there have also been reports that hormonal resuscitation is not effective, possibly as a result of higher dosage [146] and the dosage dependent effect of the hormones on mitochondria [147-149].

One successful treatment, particularly in lung transplantation, is the administration of high dose steroids before the procurement of the lung, commonly performed in the clinic [150]. Not only is the lung function under this treatment improved, but also more transplants become available by suppressing pro-inflammatory mediated cellular injury [150]. Although more preconditioning strategies are available, the most noted one is ischemic preconditioning [151], based on the work of Murry et al. [152]. He showed that repetitive short periods of ischemia reduce the extent of ischemia induced myocardial tissue injury [152].

Alternatively, another preconditioning strategy, is pharmacological preconditioning, f.i. with dopamine [153]. Dopamine is one of many catecholamines commonly used for cardiovascular support in hypotensive brain dead donors [71]. However it lost preference in the clinical routine after it failed to improve the outcome or mortality of patients with acute renal failure in the ICU [154, 155]. There were even implications for a negative systemic impact [156]. In contrast were the findings of Schnuelle et al. [153, 157, 158] that showed that brain dead donor dopamine preconditioning improved early kidney function and improved graft survival, particularly in grafts with extended cold ischemia times. In experimental studies, dopamine has an anti-inflammatory [159] but also cryoprotective effect [160]. The effect of dopamine may be either mediated by the induction of hemeoxygenase 1 [161, 162], its suggested influence on mitochondria by its redox activity [163, 164] or via the induction of H_2S production [165]. This may explain the clinical success of low dose dopamine preconditioning in kidney [166] and heart transplantation [167]. However, 12.5%

brain dead donors develop adverse side effects under treatment with dopamine. As a consequence the treatment needs to be discontinued and the potentially beneficial effect is lost [166, 167]. To circumvent this, a non-hemodynamic dopamine derivative, N-octanoyl dopamine (NOD) was developed by the group Yard et al. [163], with an increased cellular affinity as a result of its lipophilicity [163]. The cryoprotective effect of this dopamine derivative, sharing many similarities with other cryoprotective N-acyl dopamine derivatives, is superior compared to dopamine (Figure 2) [163, 168]. It is therefore likely that NOD will exert similar or even improved protection in transplantation.

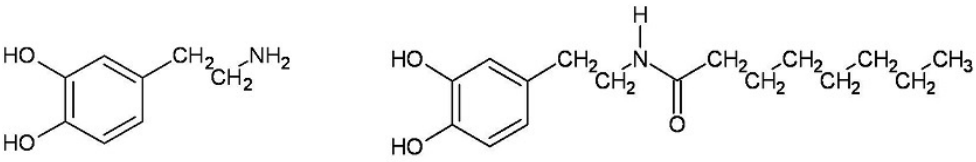

Figure 2. Dopamine (left structural formula) and N-octanoyl dopamine (right structural formula) with the lipophilic octanoic acid [163].

Aim of this Thesis

The aim of this thesis consists of two parts. Part 1 (Chapter 1-4) focusses on the effect of NOD in transplantation and related processes, while the second part (Chapter 5-8) aims to elucidate which effect two commonly used ventilation strategies and the cause of brain death have on the donor lung and kidney quality.

In contrast to the improved outcome after dopamine preconditioning in transplantation, it failed to improve outcome or mortality in acute kidney failure in the ICU. However, its synthetic lipophilic derivative N-octanoyl dopamine belongs to N-acyl-dopamine derivatives that have been described to potentially prevent and attenuate ischemia/reperfusion injury [169]. For that reason, the effect of N-octanoyl dopamine in comparison to dopamine was tested in an acute kidney injury model in *Chapter one*. Nevertheless, dopamine, the hemodynamic active precursor of NOD, was beneficial in kidney and heart transplantation as preconditioning agent [166, 167]. In *Chapter two,* it was tested whether the effect was due to prevention of cold storage induced injury and whether this was adrenceptor independently. Because NOD has a higher cell-affinity it was expected to lead to superior results compared to dopamine [163]. *Chapter three* aimed to evaluate the potential anti-inflammatory effect of N-octanoyl dopamine and to elucidate the underlying mechanism. In *Chapter two* and *three* it was investigated, which of the structural properties of NOD are needed for its cryoprotective and anti-inflammatory effect.

I

Independently of this thesis, it has been shown that NOD, as brain dead donor preconditioning, exerts in experimental kidney and heart transplantation an anti-inflammatory and cell protective effect, positively influencing acute kidney rejection [170]. Thus, *Chapter four* investigated whether NOD brain dead donor preconditioning inhibits the immune response before and after transplantation, preventing graft deterioration in a syngeneic rat lung transplantation model, since the effect of NOD might differ in various organ systems.

Recently, it has been shown that lung protective mechanical ventilation increases the number of eligible lung transplants compared to conventional mechanical ventilation [12]. However, in the comparable lung disorder acute respiratory distress syndrome [86], high tidal volume ventilation had a substantial impact on the lung and kidney *[38, 135].* Since the effect in brain death is unknown *Chapters five* and *six* elucidate the effect of high tidal volume ventilation low PEEP ventilation versus low tidal volume best PEEP ventilation (considered as lung protective) during six hours of brain death. While *Chapter five* focusses on the direct effect of different ventilation modalities on the lung, *Chapter six* focuses on the indirect effect of ventilation modalities on donor kidneys. Nevertheless, ventilation strategies are not the only possible confounders of organ function but also the etiology of brain death in kidney transplantation [171, 172]. However, there are some differences between brain dead donors which may bias these findings as for e.g. age and pre-existing health conditions. Thus, *Chapter seven* and *eight* were intended to explore whether a sudden or prolonged increase of intracranial pressure leading to brain death have a different effect on the donor lung, kidney and liver. *Chapter* seven focusses on the effect of the two brain death induction models on the lung graft, while *Chapter eight* elucidates the effect on kidney and liver grafts and investigates possible underlying mechanisms. All the results are summarized in *Chapter nine,* followed by a discussion and a future perspective.

References

1. Guild, W.R., et al., *Successful homotransplantation of the kidney in an identical twin.* Trans Am Clin Climatol Assoc, 1955. **67**: p. 167-73.
2. Reitz, B.A., et al., Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med, 1982. **306**(10): p. 557-64.
3. *A randomized clinical trial of cyclosporine in cadaveric renal transplantation.* The New England journal of medicine, 1983. **309**(14): p. 809-15.
4. *Cyclosporin a as sole immunosuppressive agent in recipients of kidney allografts from cadaver donors. Preliminary results of a European multicentre trial.* Lancet, 1982. **2**(8289): p. 57-60.
5. Lamb, K.E., S. Lodhi, and H.U. Meier-Kriesche, *Long-term renal allograft survival in the United States: a critical reappraisal.* Am J Transplant, 2011. **11**(3): p. 450-62.
6. Thiel, G., et al., *Long-term benefits and risks of cyclosporin A (sandimmun)--an analysis at 10 years.* Transplant Proc, 1994. **26**(5): p. 2493-8.
7. Hariharan, S., et al., *Improved graft survival after renal transplantation in the United States, 1988 to 1996.* N Engl J Med, 2000. **342**(9): p. 605-12.
8. Terasaki, P.I., et al., *High survival rates of kidney transplants from spousal and living unrelated donors.* N Engl J Med, 1995. **333**(6): p. 333-6.
9. Dragun, D., et al., *Ischemia-reperfusion injury in renal transplantation is independent of the immunologic background.* Kidney Int, 2000. **58**(5): p. 2166-77.
10. Ojo, A.O., et al., *Delayed graft function: risk factors and implications for renal allograft survival.* Transplantation, 1997. **63**(7): p. 968-74.
11. Pratschke, J., et al., *Accelerated rejection of renal allografts from brain-dead donors.* Ann Surg, 2000. **232**(2): p. 263-71.
12. Mascia, L., et al., *Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial.* JAMA, 2010. **304**(23): p. 2620-7.
13. de Perrot, M., et al., *Effect of ventilator-induced lung injury on the development of reperfusion injury in a rat lung transplant model.* J Thorac Cardiovasc Surg, 2002. **124**(6): p. 1137-44.
14. van der Hoeven, J.A., et al., *Relationship between duration of brain death and hemodynamic (in)stability on progressive dysfunction and increased immunologic activation of donor kidneys.* Kidney Int, 2003. **64**(5): p. 1874-82.
15. Rosendale, J.D., et al., *Aggressive pharmacologic donor management results in more transplanted organs.* Transplantation, 2003. **75**(4): p. 482-7.
16. Blasco, V., et al., *Impact of intensive care on renal function before graft harvest: results of a monocentric study.* Crit Care, 2007. **11**(5): p. R103.
17. Oto, T., et al., *Association between primary graft dysfunction among lung, kidney and heart recipients from the same multiorgan donor.* Am J Transplant, 2008. **8**(10): p. 2132-9.
18. de Perrot, M., et al., *Ischemia-reperfusion-induced lung injury.* Am J Respir Crit Care Med, 2003. **167**(4): p. 490-511.
19. Shoskes, D.A. and J.M. Cecka, *Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection.* Transplantation, 1998. **66**(12): p. 1697-701.
20. Orens, J.B., et al., *A review of lung transplant donor acceptability criteria.* J Heart Lung Transplant, 2003. **22**(11): p. 1183-200.
21. Koning, O.H., et al., *Risk factors for delayed graft function in cadaveric kidney transplantation: a prospective study of renal function and graft survival after preservation with University of Wisconsin solution in multi-organ donors. European Multicenter Study Group.* Transplantation, 1997. **63**(11): p. 1620-8.
22. Detry, O., et al., *Categories of donation after cardiocirculatory death.* Transplant Proc, 2012. **44**(5): p. 1189-95.
23. McKeating, E.G., et al., *Transcranial cytokine gradients in patients requiring intensive care after acute brain injury.* Br J Anaesth, 1997. **78**(5): p. 520-3.
24. Pelinka, L.E., et al., *GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome.* J Neurotrauma, 2004. **21**(11): p. 1553-61.

I

25. Fisher, A.J., et al., *Enhanced pulmonary inflammation in organ donors following fatal non-traumatic brain injury.* Lancet, 1999. **353**(9162): p. 1412-3.
26. Fujishima, S. and N. Aikawa, *Neutrophil-mediated tissue injury and its modulation.* Intensive Care Med, 1995. **21**(3): p. 277-85.
27. Mascia, L. and P.J. Andrews, *Acute lung injury in head trauma patients.* Intensive Care Med, 1998. **24**(10): p. 1115-6.
28. Mehta, R.L., et al., *Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury.* Crit Care, 2007. **11**(2): p. R31.
29. Moore, E.M., et al., *The incidence of acute kidney injury in patients with traumatic brain injury.* Ren Fail, 2010. **32**(9): p. 1060-5.
30. Li, N., W.G. Zhao, and W.F. Zhang, *Acute kidney injury in patients with severe traumatic brain injury: implementation of the acute kidney injury network stage system.* Neurocrit Care, 2011. **14**(3): p. 377-81.
31. Simmons, R.L., et al., *Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury.* Ann Surg, 1969. **170**(1): p. 39-44.
32. Baumann, A., et al., *Neurogenic pulmonary edema.* Acta Anaesthesiol Scand, 2007. **51**(4): p. 447-55.
33. Rogers, F.B., et al., *Neurogenic pulmonary edema in fatal and nonfatal head injuries.* J Trauma, 1995. **39**(5): p. 860-6; discussion 866-8.
34. Maniatis, N.A. and S.E. Orfanos, *The endothelium in acute lung injury/acute respiratory distress syndrome.* Curr Opin Crit Care, 2008. **14**(1): p. 22-30.
35. Yildirim, E., et al., *Ultrastructural changes in pneumocyte type II cells following traumatic brain injury in rats.* Eur J Cardiothorac Surg, 2004. **25**(4): p. 523-9.
36. Dreyfuss, D., et al., *High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure.* Am Rev Respir Dis, 1988. **137**(5): p. 1159-64.
37. Liu, Y.Y., et al., *Spillover of Cytokines and Reactive Oxygen Species in Ventilator-Induced Lung Injury Associated With Inflammation and Apoptosis in Distal Organs.* Respir Care, 2014.
38. Imai, Y., et al., *Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome.* JAMA, 2003. **289**(16): p. 2104-12.
39. Chen, E.P., et al., *Hormonal and hemodynamic changes in a validated animal model of brain death.* Crit Care Med, 1996. **24**(8): p. 1352-9.
40. Smith, M., *Physiologic changes during brain stem death--lessons for management of the organ donor.* J Heart Lung Transplant, 2004. **23**(9 Suppl): p. S217-22.
41. Wood, K.E., et al., *Care of the potential organ donor.* N Engl J Med, 2004. **351**(26): p. 2730-9.
42. Shivalkar, B., et al., *Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function.* Circulation, 1993. **87**(1): p. 230-9.
43. Cooper, D.K., D. Novitzky, and W.N. Wicomb, *Hormonal therapy in the brain-dead experimental animal.* Transplant Proc, 1988. **20**(5 Suppl 7): p. 51-4.
44. Cooper, D.K., D. Novitzky, and W.N. Wicomb, *The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart.* Ann R Coll Surg Engl, 1989. **71**(4): p. 261-6.
45. Powner, D.J., et al., *Changes in serum catecholamine levels in patients who are brain dead.* J Heart Lung Transplant, 1992. **11**(6): p. 1046-53.
46. Bittner, H.B., et al., *Myocardial beta-adrenergic receptor function and high-energy phosphates in brain death--related cardiac dysfunction.* Circulation, 1995. **92**(9 Suppl): p. II472-8.
47. Bittner, H.B., et al., *Myocardial performance after graft preservation and subsequent cardiac transplantation from brain-dead donors.* Ann Thorac Surg, 1995. **60**(1): p. 47-54.
48. Brouwers, P.J., et al., *Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage.* Stroke, 1989. **20**(9): p. 1162-7.
49. Di Pasquale, G., et al., *Holter detection of cardiac arrhythmias in intracranial subarachnoid hemorrhage.* Am J Cardiol, 1987. **59**(6): p. 596-600.
50. Avlonitis, V.S., et al., *The hemodynamic mechanisms of lung injury and systemic inflammatory response following brain death in the transplant donor.* Am J Transplant, 2005. **5**(4 Pt 1): p. 684-93.
51. Novitzky, D., et al., *Pathophysiology of pulmonary edema following experimental brain death in the chacma baboon.* Ann Thorac Surg, 1987. **43**(3): p. 288-94.

52. Theodore, J. and E.D. Robin, *Speculations on neurogenic pulmonary edema (NPE).* Am Rev Respir Dis, 1976. **113**(4): p. 405-11.
53. Bugge, J.F., *Brain death and its implications for management of the potential organ donor.* Acta Anaesthesiol Scand, 2009. **53**(10): p. 1239-50.
54. Bittner, H.B., et al., *A valid experimental brain death organ donor model.* J Heart Lung Transplant, 1995. **14**(2): p. 308-17.
55. Bittner, H.B., et al., *Endocrine changes and metabolic responses in a validated canine brain death model.* J Crit Care, 1995. **10**(2): p. 56-63.
56. Szabo, G., et al., *Modulation of coronary perfusion pressure can reverse cardiac dysfunction after brain death.* Ann Thorac Surg, 1999. **67**(1): p. 18-25; discussion 25-6.
57. Pennefather, S.H., R.E. Bullock, and J.H. Dark, *The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors.* Transplantation, 1993. **56**(6): p. 1418-22.
58. Van Raemdonck, D., et al., *Lung donor selection and management.* Proc Am Thorac Soc, 2009. **6**(1): p. 28-38.
59. Ueno, T., C. Zhi-Li, and T. Itoh, *Unique circulatory responses to exogenous catecholamines after brain death.* Transplantation, 2000. **70**(3): p. 436-40.
60. Rostron, A.J., et al., *Hemodynamic resuscitation with arginine vasopressin reduces lung injury after brain death in the transplant donor.* Transplantation, 2008. **85**(4): p. 597-606.
61. Novitzky, D., et al., *Electrocardiographic and histopathologic changes developing during experimental brain death in the baboon.* Transplant Proc, 1989. **21**(1 Pt 3): p. 2567-9.
62. Novitzky, D., et al., *Improved cardiac function following hormonal therapy in brain dead pigs: relevance to organ donation.* Cryobiology, 1987. **24**(1): p. 1-10.
63. Wicomb, W.N., et al., *The effects of brain death and 24 hours' storage by hypothermic perfusion on donor heart function in the pig.* J Thorac Cardiovasc Surg, 1986. **91**(6): p. 896-909.
64. Arita, K., et al., *The function of the hypothalamo-pituitary axis in brain dead patients.* Acta Neurochir (Wien), 1993. **123**(1-2): p. 64-75.
65. Sugimoto, T., et al., *Morphological and functional alterations of the hypothalamic-pituitary system in brain death with long-term bodily living.* Acta Neurochir (Wien), 1992. **115**(1-2): p. 31-6.
66. Herijgers, P., et al., *Changes in organ perfusion after brain death in the rat and its relation to circulating catecholamines.* Transplantation, 1996. **62**(3): p. 330-5.
67. Flowers, W.M., Jr. and B.R. Patel, *Radionuclide angiography as a confirmatory test for brain death: a review of 229 studies in 219 patients.* South Med J, 1997. **90**(11): p. 1091-6.
68. Schroder, R., *Later changes in brain death. Signs of partial recirculation.* Acta Neuropathol, 1983. **62**(1-2): p. 15-23.
69. Novitzky, D., et al., *Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy.* Transplantation, 1988. **45**(1): p. 32-6.
70. Mandel, L.J., R. Bacallao, and G. Zampighi, *Uncoupling of the molecular 'fence' and paracellular 'gate' functions in epithelial tight junctions.* Nature, 1993. **361**(6412): p. 552-5.
71. McKeown, D.W., R.S. Bonser, and J.A. Kellum, *Management of the heartbeating brain-dead organ donor.* Br J Anaesth, 2012. **108 Suppl 1**: p. i96-107.
72. Bello, G., et al., *The role of thyroid dysfunction in the critically ill: a review of the literature.* Minerva Anestesiol, 2010. **76**(11): p. 919-28.
73. Klein, I. and K. Ojamaa, *Thyroid hormone: targeting the vascular smooth muscle cell.* Circ Res, 2001. **88**(3): p. 260-1.
74. Amado, J.A., et al., *Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants.* Metabolism, 1995. **44**(6): p. 812-6.
75. Takada, M., et al., *Effects of explosive brain death on cytokine activation of peripheral organs in the rat.* Transplantation, 1998. **65**(12): p. 1533-42.
76. Walko, T.D., 3rd, et al., *Cerebrospinal fluid mitochondrial DNA: a novel DAMP in pediatric traumatic brain injury.* Shock, 2014. **41**(6): p. 499-503.
77. Cohen, M.J., et al., *Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion.* Crit Care, 2009. **13**(6): p. R174.
78. Zhang, Q., et al., *Circulating mitochondrial DAMPs cause inflammatory responses to injury.* Nature, 2010. **464**(7285): p. 104-7.

I

79. Sun, S., et al., *Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways.* PLoS One, 2013. **8**(3): p. e59989.
80. Weber, D.J., et al., *The HMGB1-RAGE axis mediates traumatic brain injury-induced pulmonary dysfunction in lung transplantation.* Sci Transl Med, 2014. **6**(252): p. 252ra124.
81. Prekker, M.E., et al., *Early Trends in PaO(2)/fraction of inspired oxygen ratio predict outcome in lung transplant recipients with severe primary graft dysfunction.* Chest, 2007. **132**(3): p. 991-7.
82. Kruger, B., et al., *Donor Toll-like receptor 4 contributes to ischemia and reperfusion injury following human kidney transplantation.* Proc Natl Acad Sci U S A, 2009. **106**(9): p. 3390-5.
83. Yu, M., et al., *HMGB1 signals through toll-like receptor (TLR) 4 and TLR2.* Shock, 2006. **26**(2): p. 174-9.
84. Morariu, A.M., et al., *Early events in kidney donation: progression of endothelial activation, oxidative stress and tubular injury after brain death.* Am J Transplant, 2008. **8**(5): p. 933-41.
85. Faropoulos, K. and E. Apostolakis, *Brain death and its influence on the lungs of the donor: how is it prevented?* Transplant Proc, 2009. **41**(10): p. 4114-9.
86. Fisher, A.J., et al., *Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation.* Am J Respir Crit Care Med, 2001. **163**(1): p. 259-65.
87. Okamoto, S., et al., *Role of hypotension in brain-death associated impairment of liver microcirculation and viability.* Transpl Int, 2000. **13**(6): p. 428-35.
88. Nekludov, M., et al., *Coagulation abnormalities associated with severe isolated traumatic brain injury: cerebral arterio-venous differences in coagulation and inflammatory markers.* J Neurotrauma, 2007. **24**(1): p. 174-80.
89. Lisman, T., et al., *Activation of hemostasis in brain dead organ donors: an observational study.* J Thromb Haemost, 2011. **9**(10): p. 1959-65.
90. Oto, T., et al., *Unexpected donor pulmonary embolism affects early outcomes after lung transplantation: a major mechanism of primary graft failure?* J Thorac Cardiovasc Surg, 2005. **130**(5): p. 1446.
91. Oto, T., et al., *The implications of pulmonary embolism in a multiorgan donor for subsequent pulmonary, renal, and cardiac transplantation.* J Heart Lung Transplant, 2008. **27**(1): p. 78-85.
92. Kaneda, H., et al., *Pre-implantation multiple cytokine mRNA expression analysis of donor lung grafts predicts survival after lung transplantation in humans.* Am J Transplant, 2006. **6**(3): p. 544-51.
93. de Perrot, M. and S. Keshavjee, *Lung transplantation. Lung preservation.* Chest Surg Clin N Am, 2003. **13**(3): p. 443-62.
94. Taylor, D.O., et al., *Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report--2008.* J Heart Lung Transplant, 2008. **27**(9): p. 943-56.
95. Christie, J.D., et al., *Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation.* J Heart Lung Transplant, 2005. **24**(10): p. 1454-9.
96. Lee, J.C. and J.D. Christie, *Primary graft dysfunction.* Proc Am Thorac Soc, 2009. **6**(1): p. 39-46.
97. Fisher, A.J., et al., *Non-immune acute graft injury after lung transplantation and the risk of subsequent bronchiolitis obliterans syndrome (BOS).* J Heart Lung Transplant, 2002. **21**(11): p. 1206-12.
98. Weinberg, J.M., *The cell biology of ischemic renal injury.* Kidney Int, 1991. **39**(3): p. 476-500.
99. Wakayama, K., et al., *Successful transplantation of rat hearts subjected to extended cold preservation with a novel preservation solution.* Transpl Int, 2012. **25**(6): p. 696-706.
100. den Hengst, W.A., et al., *Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process.* Am J Physiol Heart Circ Physiol, 2010. **299**(5): p. H1283-99.
101. Cross, H.R., G.K. Radda, and K. Clarke, *The role of Na+/K+ ATPase activity during low flow ischemia in preventing myocardial injury: a 31P, 23Na and 87Rb NMR spectroscopic study.* Magn Reson Med, 1995. **34**(5): p. 673-85.
102. Rasola, A. and P. Bernardi, *Mitochondrial permeability transition in Ca(2+)-dependent apoptosis and necrosis.* Cell Calcium, 2011. **50**(3): p. 222-33.
103. Guzy, R.D., et al., *Mitochondrial complex III is required for hypoxia-induced ROS production and cellular oxygen sensing.* Cell Metab, 2005. **1**(6): p. 401-8.
104. Vanden Hoek, T.L., et al., *Significant levels of oxidants are generated by isolated cardiomyocytes during ischemia prior to reperfusion.* J Mol Cell Cardiol, 1997. **29**(9): p. 2571-83.
105. Dennis, S.C., W. Gevers, and L.H. Opie, *Protons in ischemia: where do they come from; where do they go to?* J Mol Cell Cardiol, 1991. **23**(9): p. 1077-86.

106. Huang, H. and A.K. Salahudeen, *Cold induces catalytic iron release of cytochrome P-450 origin: a critical step in cold storage-induced renal injury.* American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 2002. **2**(7): p. 631-9.
107. Bysani, G.K., et al., *Role of cytochrome P-450 in reperfusion injury of the rabbit lung.* J Clin Invest, 1990. **86**(5): p. 1434-41.
108. Fischer, S., et al., *Cell death in human lung transplantation: apoptosis induction in human lungs during ischemia and after transplantation.* Ann Surg, 2000. **231**(3): p. 424-31.
109. Kaczmarek, A., P. Vandenabeele, and D.V. Krysko, *Necroptosis: the release of damage-associated molecular patterns and its physiological relevance.* Immunity, 2013. **38**(2): p. 209-23.
110. Guth, S., et al., *Length of pressure-controlled reperfusion is critical for reducing ischaemia-reperfusion injury in an isolated rabbit lung model.* J Cardiothorac Surg, 2007. **2**: p. 54.
111. Bhabra, M.S., et al., *Critical importance of the first 10 minutes of lung graft reperfusion after hypothermic storage.* Ann Thorac Surg, 1996. **61**(6): p. 1631-5.
112. Bhabra, M.S., et al., *Controlled reperfusion protects lung grafts during a transient early increase in permeability.* Ann Thorac Surg, 1998. **65**(1): p. 187-92.
113. Halldorsson, A.O., et al., *Controlled reperfusion prevents pulmonary injury after 24 hours of lung preservation.* Ann Thorac Surg, 1998. **66**(3): p. 877-84; discussion 884-5.
114. Halldorsson, A.O., et al., *Lowering reperfusion pressure reduces the injury after pulmonary ischemia.* Ann Thorac Surg, 2000. **69**(1): p. 198-203; discussion 204.
115. Lick, S.D., et al., *Technique of controlled reperfusion of the transplanted lung in humans.* Ann Thorac Surg, 2000. **69**(3): p. 910-2.
116. Ross, S.D., et al., *Reduced neutrophil infiltration protects against lung reperfusion injury after transplantation.* Ann Thorac Surg, 1999. **67**(5): p. 1428-33; discussion 1434.
117. Naidu, B.V., et al., *Early activation of the alveolar macrophage is critical to the development of lung ischemia-reperfusion injury.* J Thorac Cardiovasc Surg, 2003. **126**(1): p. 200-7.
118. Allen, B.S., *The role of leukodepletion in limiting ischemia/reperfusion damage in the heart, lung and lower extremity.* Perfusion, 2002. **17 Suppl**: p. 11-22.
119. Eppinger, M.J., et al., *Pattern of injury and the role of neutrophils in reperfusion injury of rat lung.* J Surg Res, 1995. **58**(6): p. 713-8.
120. Eppinger, M.J., et al., *Mediators of ischemia-reperfusion injury of rat lung.* Am J Pathol, 1997. **150**(5): p. 1773-84.
121. Fiser, S.M., et al., *Lung transplant reperfusion injury involves pulmonary macrophages and circulating leukocytes in a biphasic response.* J Thorac Cardiovasc Surg, 2001. **121**(6): p. 1069-75.
122. Ilmakunnas, M., et al., *High mobility group box 1 protein as a marker of hepatocellular injury in human liver transplantation.* Liver Transpl, 2008. **14**(10): p. 1517-25.
123. Tsung, A., et al., *The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion.* J Exp Med, 2005. **201**(7): p. 1135-43.
124. Moore, T.M., et al., *Adhesion molecules contribute to ischemia and reperfusion-induced injury in the isolated rat lung.* J Appl Physiol (1985), 1995. **78**(6): p. 2245-52.
125. DeMeester, S.R., et al., *Attenuation of rat lung isograft reperfusion injury with a combination of anti-ICAM-1 and anti-beta2 integrin monoclonal antibodies.* Transplantation, 1996. **62**(10): p. 1477-85.
126. Adoumie, R., et al., *Early cellular events in the lung allograft.* Ann Thorac Surg, 1992. **54**(6): p. 1071-6; discussion 1076-7.
127. de Perrot, M., et al., *Recipient T cells mediate reperfusion injury after lung transplantation in the rat.* J Immunol, 2003. **171**(10): p. 4995-5002.
128. Avlonitis, V.S., et al., *Pulmonary transplantation: the role of brain death in donor lung injury.* Transplantation, 2003. **75**(12): p. 1928-33.
129. Lee, J.C. and J.D. Christie, *Primary graft dysfunction.* Clin Chest Med, 2011. **32**(2): p. 279-93.
130. Esme, H., et al., *Effect of lung ischemia--reperfusion on oxidative stress parameters of remote tissues.* Eur J Cardiothorac Surg, 2006. **29**(3): p. 294-8.
131. Bratton, S.L. and R.L. Davis, *Acute lung injury in isolated traumatic brain injury.* Neurosurgery, 1997. **40**(4): p. 707-12; discussion 712.

I

132. Chaparro, C., et al., *Acute lung injury in lung allografts.* J Heart Lung Transplant, 1995. **14**(2): p. 267-73.
133. Trulock, E.P., *Lung transplantation.* Am J Respir Crit Care Med, 1997. **155**(3): p. 789-818.
134. Gattinoni, L. and A. Pesenti, *The concept of "baby lung".* Intensive Care Med, 2005. **31**(6): p. 776-84.
135. *Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.* N Engl J Med, 2000. **342**(18): p. 1301-8.
136. Darby, J.M., et al., *Approach to management of the heartbeating 'brain dead' organ donor.* JAMA, 1989. **261**(15): p. 2222-8.
137. Bos, E.M., et al., *Kidney grafts from brain dead donors: Inferior quality or opportunity for improvement?* Kidney Int, 2007. **72**(7): p. 797-805.
138. Cohen, B. and G.G. Persijn, *Trends in organ donation.* Transplant Proc, 1997. **29**(8): p. 3301-2.
139. Novick, R.J., et al., *Influence of graft ischemic time and donor age on survival after lung transplantation.* J Heart Lung Transplant, 1999. **18**(5): p. 425-31.
140. Christie, J.D., et al., *Clinical risk factors for primary graft failure following lung transplantation.* Chest, 2003. **124**(4): p. 1232-41.
141. Ojo, A.O., *Expanded criteria donors: process and outcomes.* Semin Dial, 2005. **18**(6): p. 463-8.
142. Munro, J.M. and R.S. Cotran, *The pathogenesis of atherosclerosis: atherogenesis and inflammation.* Lab Invest, 1988. **58**(3): p. 249-61.
143. Novitzky, D., D.K. Cooper, and B. Reichart, *Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors.* Transplantation, 1987. **43**(6): p. 852-4.
144. Novitzky, D., et al., *Triiodothyronine therapy for heart donor and recipient.* J Heart Transplant, 1988. **7**(5): p. 370-6.
145. Rosendale, J.D., et al., *Hormonal resuscitation yields more transplanted hearts, with improved early function.* Transplantation, 2003. **75**(8): p. 1336-41.
146. Meyers, C.H., et al., *Effects of triiodothyronine and vasopressin on cardiac function and myocardial blood flow after brain death.* J Heart Lung Transplant, 1993. **12**(1 Pt 1): p. 68-79; discussion 79-80.
147. de Lange, P., et al., *Uncoupling protein-3 is a molecular determinant for the regulation of resting metabolic rate by thyroid hormone.* Endocrinology, 2001. **142**(8): p. 3414-20.
148. Lanni, A., et al., *Thyroid hormone and uncoupling proteins.* FEBS Lett, 2003. **543**(1-3): p. 5-10.
149. Pedersen, S.B., et al., *Insulin and contraction directly stimulate UCP2 and UCP3 mRNA expression in rat skeletal muscle in vitro.* Biochem Biophys Res Commun, 2001. **283**(1): p. 19-25.
150. Follette, D.M., S.M. Rudich, and W.D. Babcock, *Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death.* J Heart Lung Transplant, 1998. **17**(4): p. 423-9.
151. Gasparri, R.I., et al., *Ischemic preconditioning enhances donor lung preservation in the rabbit.* Eur J Cardiothorac Surg, 1999. **16**(6): p. 639-46.
152. Murry, C.E., R.B. Jennings, and K.A. Reimer, *Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.* Circulation, 1986. **74**(5): p. 1124-36.
153. Schnuelle, P., et al., *Impact of donor dopamine on immediate graft function after kidney transplantation.* American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 2004. **4**(3): p. 419-26.
154. Kellum, J.A. and M.D. J, *Use of dopamine in acute renal failure: a meta-analysis.* Crit Care Med, 2001. **29**(8): p. 1526-31.
155. Bellomo, R., et al., *Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group.* Lancet, 2000. **356**(9248): p. 2139-43.
156. Holmes, C.L. and K.R. Walley, *Bad medicine: low-dose dopamine in the ICU.* Chest, 2003. **123**(4): p. 1266-75.
157. Schnuelle, P., et al., *Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation.* Kidney international, 1999. **56**(2): p. 738-46.
158. Schnuelle, P., et al., *Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation.* Transplantation, 2001. **72**(3): p. 455-63.

159. Kapper, S., et al., *Modulation of chemokine production and expression of adhesion molecules in renal tubular epithelial and endothelial cells by catecholamines.* Transplantation, 2002. **74**(2): p. 253-60.
160. Yard, B., et al., *Prevention of cold-preservation injury of cultured endothelial cells by catecholamines and related compounds.* American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 2004. **4**(1): p. 22-30.
161. Berger, S.P., et al., *Dopamine induces the expression of heme oxygenase-1 by human endothelial cells in vitro.* Kidney international, 2000. **58**(6): p. 2314-9.
162. Salahudeen, A.A., et al., *Overexpression of heme oxygenase protects renal tubular cells against cold storage injury: studies using hemin induction and HO-1 gene transfer.* Transplantation, 2001. **72**(9): p. 1498-504.
163. Losel, R.M., et al., *N-octanoyl dopamine, a non-hemodyanic dopamine derivative, for cell protection during hypothermic organ preservation.* PLoS One, 2010. **5**(3): p. e9713.
164. Brinkkoetter, P.T., et al., *Hypothermic injury: the mitochondrial calcium, ATP and ROS love-hate triangle out of balance.* Cell Physiol Biochem, 2008. **22**(1-4): p. 195-204.
165. Talaei, F., et al., *Serotonin and dopamine protect from hypothermia/rewarming damage through the CBS/H2S pathway.* PLoS One, 2011. **6**(7): p. e22568.
166. Schnuelle, P., et al., *Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial.* JAMA, 2009. **302**(10): p. 1067-75.
167. Benck, U., et al., *Effects of donor pre-treatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial.* J Am Coll Cardiol, 2011. **58**(17): p. 1768-77.
168. Wedel, J., et al., *N-acyl dopamine derivates as lead compound for implementation in transplantation medicine.* Transplant Rev (Orlando), 2014.
169. Zhong, B. and D.H. Wang, *N-oleoyldopamine, a novel endogenous capsaicin-like lipid, protects the heart against ischemia-reperfusion injury via activation of TRPV1.* Am J Physiol Heart Circ Physiol, 2008. **295**(2): p. H728-35.
170. Spindler, R.S., et al., *N-Octanoyl Dopamine for Donor Treatment in a Brain-Death Model of Kidney and Heart Transplantation.* Transplantation, 2015.
171. Pessione, F., et al., *Multivariate analysis of donor risk factors for graft survival in kidney transplantation.* Transplantation, 2003. **75**(3): p. 361-7.
172. Zukowski, M., et al., *Cause of death in multiorgan donors and its relation to the function of transplanted kidneys.* Transplant Proc, 2009. **41**(8): p. 2972-4.