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### Brain death: from inflammation to metabolic changes

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**SUMMARY  
CONCLUSION  
AND FUTURE PERSPECTIVES**

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## SUMMARY AND CONCLUSION

Organ transplantation is an excellent therapeutic opportunity for end-stage organ failure. However the amount of organs for donation is still low compared with the waiting list. Increasing the number of organs suitable for transplantation is one of the mayor tasks for the community in this field. The aim of this thesis was to explore new aspects of brain dead donation and alternatives to improve quality and number of available organs for transplantation, with focus on liver and kidney grafts.

The current text is divided in two parts, first there is a group of three experiments related with inflammation and hormonal interventions in brain dead (BD) rats, focusing in the quality of liver and kidney, then a fourth experiment comparing two models of brain death. Second part, a group of three experiments describing the metabolic changes during BD.

In the second chapter we tested the effect of Prednisolone given before BD induction. Interestingly we found a better kidney function, measured by Creatinine plasma levels, in BD treated animals, but no difference in liver cell injury markers (AST and ALT). Notoriously, inflammation was blocked in BD prednisolone treated animals. However complement system seems active in the liver but not in the kidney of those animals. We hypothesized that complement system activation could explain liver cell injury in brain dead rats treated with Prednisolone. The third chapter includes the results of Prednisolone treatment in BD rats administered after BD induction. In this case we did not find better creatinine plasma levels in those treated animals, nor difference in liver cell injury markers. As in our previous experiment in this case we found a strong anti-inflammatory response to the Prednisolone treatment but complement system remains active in kidney and liver tissue. Thus we hypothesize that part of the injury occurs during BD induction that activates complement system, and this could be a key player in the BD-induced injury later on.

We tested 3,3',5-triiodo-L-thyronine ( $T_3$ ) as a preconditioning agent in order to improve the quality of the liver after BD (chapter four). We found a decrease in plasma liver cell injury markers and in pro-apoptotic markers in the liver tissue of  $T_3$  treated BD rats. However this treatment did not improve creatinine plasma levels. Interestingly, these effects were not associated with any anti-inflammatory effect. Thus, we hypothesize that BD-induced Inflammation may be an important key player for cellular injury during BD, but not the only key player. Since treatments that do not modify the inflammatory response can reduce apoptotic markers.

As we investigated in these previous chapters the effect of hormonal and inflammatory response during BD, in the fifth chapter we assessed the relationship between hemodynamic profiles and organ quality during BD. We described the differences between fast and slow onset of BD. We compared these two models of BD and their hemodynamic profiles, focusing on inflammation and organ quality. Fast induction was characterized by a sudden increase in blood pressure during BD onset and a pronounced hemodynamic instability later on. Contrary, slow induction model characterized by a hypotensive period

just before BD onset but less volume and vasopressor requirement during the BD period. In regards of kidney and liver injury, both organs were damaged but the kidney was strongly damaged in the slow induction model compared to fast induction model. This has shown us that a different hemodynamic profile could affect importantly to kidney but seems to be a less important factor to liver.

From this first part we can conclude that despite hemodynamic stability and anti-inflammatory treatments, brain death is affecting kidney and liver quality. Each key elements in BD pathophysiology act in conjoint fashion to determine organ quality, we hypothesized that these elements are affecting cellular metabolism, energy production and finally, cell survival. In the second part we addressed that hypothesis.

As in others pathological conditions (e.g Sepsis): hemodynamic, hormonal and inflammatory changes affect cell metabolism, we described (chapter six) some changes in carbohydrates and fatty acid metabolism. Also we found that glycolysis seems mainly active while gluconeogenesis seems to be suppressed in hepatic and renal tissue of BD animals compared to sham operated animals. Moreover, an exhaustion of carbohydrates hepatic storage is present in brain dead animals associated to lower glucose plasma levels and higher lactate plasma levels. More over an increase in fatty acid oxidation seems to be present in BD animals. These changes could be related to a poor tissue oxygen delivery, thus in the seventh chapter we describe oxygen consumption and organ perfusion in BD rats using magnetic resonance imaging assessment. We found that liver oxygen consumption is increased while blood flow is preserved. Contrary, kidney oxygen consumption is preserved while blood flow is decreased in brain dead animals. Interestingly these results shown, again, that liver and kidney are facing different problems, while kidney in suffering from ischemic injury the liver seems to be actively consuming oxygen.

Since the final oxygen consumer within the cell is mitochondria, in the eighth chapter there is a complementary experience describing mitochondrial oxygen consumption in isolated mitochondria from liver and kidney of brain dead animals. An increase in the uncouple state was found in these isolated mitochondria, associated with a higher oxidative capacity. Interestingly no real mitochondria dysfunction was found in this experience, it seems more like an adaptive response to a higher energetic demand and secondary oxidative stress during brain death.

These results together, can be interpreted as a new level of complexity in brain death donation. The transplant community could consider explore new treatments. Improve metabolic or nutritional status of brain dead donors as we showed lower levels of plasma glucose and increased fatty acid oxidation or decide to treat organs in an isolated fashion using machines perfusion allowing optimization of pressure, fluids, nutrients or repairing specific injuries. This thesis aimed to shed some light into these topics, showing that hemodynamic control and anti-inflammatory treatments are not enough for improving graft quality but also showing differences in liver and kidney metabolic response and organ perfusion during brain death.

## **FUTURE PERSPECTIVES**

As we previously mention new treatments or managements are needed for BD donors in order to improve future graft quality. We think that there are at least two interesting areas: (i) BD multi-organ donor care and (ii) isolated perfused organs care.

As we shown, despite normal mean arterial pressure, kidney tissue has a reduced blood flow during BD. An interesting opportunity could be to study blood flow changes during BD using a renal vasodilators acting in the Renin-Angiotensin- Aldosterone axis antagonizing catecholamines effects, in order to improve renal perfusion and eventually graft quality.

Also, we think that a better availability of nutrients as glucose, amino and fatty acid could improve liver performance during BD. As we described in the second part of this thesis, liver is consuming oxygen actively associated with a shift to fatty acid oxidation apparently due to a decrease in carbohydrates storage. By given proper nutrition we could decrease catabolism and cellular injury in liver grafts.

However, a better approach for a BD multi-organ donor management probably should include nutritional, hemodynamic and anti-inflammatory care, so it will be the combination of strategies that could improve grafts quality.

An alternative to the multi-organ donor care, is the perfusion machines for isolated organs. These, theoretically, allow to the medical team, test the quality of the organs in an ex-vivo fashion and potentially treat specific problems in the graft. In order to achieve these goals, research should focus on metabolic changes in isolated organs. We think that graft metabolic behavior needs to be assessed in front of changes in nutrition during perfusion. In other words, perfusion solution should be adapted to the graft metabolic needs. These are exciting and open problems in the field, that we plan to explore.



