

Thermal homeostasis and liver transplantation

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Abstract. Thermal homeostasis represents the major issue during liver transplantation (OLT) since severe hypothermia may have a deleterious effect on both liver recipient organism and postoperative graft functioning. Because of the known negative influence of hypothermia on intraoperative cardiovascular activity and coagulation system, numerous methods have been suggested to reduce intraoperative heat loss and promote active warming (continuous temperature monitoring, external heat sources, improvement in surgical technique and technologies). A good intraoperative OLT course has an obvious influence on post OLT graft function recovery, but thermal homeostasis has also an essential direct effect on the graft as a constitutive component of conventional cold preservation methods. Hypothermia, however, contributes directly to the graft ischemia-reperfusion injury particularly in marginal and partial organs by several angiogenic mechanisms. For these reasons, on the light of the development of new strategies to increase the donor pool, clinical research is focusing on new preservation methods such as extracorporeal circuits with normothermic oxygenated perfusion.

Key words: Hypothermia, liver transplantation, graft

Introduction

Liver transplantation (OLT) currently represents the best therapy for end stage liver disease.

The improvement in OLT results in the last two decades was mainly due to the improvement in several fields of OLT patho-physiological knowledge such as immunosuppression, graft preservation, anaesthesiology and intensive care support, new surgical and anaesthesiological technologies. Among the wide spectrum of patho-physiological aspects involved during OLT, thermal homeostasis gains a crucial role since it influences critically both the liver recipient organism during OLT and the liver graft preservation.

Thermal homeostasis and liver recipient organism

OLT candidate has generally hemodynamic and haemostatic problems due to the hepatic disease which may be exponentially increased by a very difficult surgical procedure such as OLT.

The main patho-physiological risks during OLT are in fact intraoperative bleeding favoured by haemostatic disorders, hemodynamic instability and postreperfusion syndrome.

Severe hypothermia may potentially have a critical role in determining all these events:

1. Hypothermia contributes to the hemorrhagic diathesis during OLT: the series of enzymatic reactions of the coagulation cascade are in fact

- strongly inhibited by hypothermia (1) which may also determine reduction of platelets number and activity (2).
2. Hypothermia may contribute to hemodynamic instability during OLT determining cardiac arrhythmias and coronary and systemic vascular constriction (3).
 3. Hypothermia has been implicated in the cause of postreperfusion syndrome (4). Support for this hypothesis includes the demonstration of temperature dependent changes in cardiac function, rate and rhythm and an increase in the potential for cardiotoxicity of hyperkalemia caused by hypothermia (5).

Intra-operative hypothermia mainly results from heat loss exceeding metabolic heat production (6). Factors contributing to hypothermia during OLT include prolonged surgery, a large abdominal wound, massive transfusion, removal of a metabolically active liver and the use of a veno-venous bypass circuit (7). Veno-venous bypass, in particular, directly contributes to decrease in core temperature by approximately 0.75°C/hour; moreover it significantly increases the operative time and consequently the heat loss due to prolonged surgery (7).

The main prevention measure of intra-operative hypothermia is an accurate continuous monitoring of core temperature together with hemodynamic parameters by the use of thermocouples on the surface of Swan Ganz and femoral artery catheters. Other important measures to maintain body temperature are external heat sources: a high theatre temperature (8), warming systems placed on the body skin surface (electric and air convect warming systems, heated water blanket under the patient, wrapping the patient's arms and legs in gamgee surrounded by polythene) (9), a warming breathing system, heated fluids infused by rapid infusion systems (RIS). RIS in particular has gained a crucial role in controlling hemodynamic stability and thermal homeostasis during OLT (10, 11). The improvement in surgical technique and technologies in recent years has also favoured a decreased heat loss risk during OLT:

1. The routine application of the Piggy back procedure is associated with shorter anhepatic phase, total operating time and lower blood

products, all known factors favouring hypothermia during OLT (12, 13).

2. The use of heat exchanger permits a selective use of veno-venous bypass circuit limiting the risk of severe hypothermia (7).
3. Improvement in haemostatic control technologies (Argon beam coagulator, bipolar pliers, etc..) has brought to a decrease in blood loss and consequently in the risk of hypothermia occurrence.

Thermal homeostasis and liver graft preservation

Optimum function of the graft depends on optimal preservation after retrieval. The ischemia-reperfusion injury of the liver graft, in fact, is the major cause of primary non function following OLT (14). Hypothermia has long been considered to be an essential component of organ preservation because it prolongs the period during which anoxic cells can retain essential metabolic functions. Clinical hypothermia in different preservative solutions, consequently, is the most common method for graft storage (15). It has been shown, in fact, that 4°C is the optimal temperature for liver preservation and that a slight temperature change, even 0° to 5°C, can affect the liver graft function (16). Several studies, however, have shown that hypothermia has a crucial role in the ischemia-reperfusion injury of the graft mainly by angiogenic mechanisms:

1. Hypothermia can directly induce cell injury due to influx of sodium and chloride followed by secondary alterations of cellular calcium homeostasis and cell swelling. Sinusoidal endothelial cells (SECs) are more susceptible to cold ischemia injury than hepatocytes, however. A short period of ischemia (30 minutes) is needed, in fact, to produce apoptosis of SECs (14).
2. Early postoperative liver function is directly related to the extent of platelet adhesion that occurs on reperfusion. Hypothermia increases SECs expression of the platelet receptor - Von Willebrand factor which determines an increased platelet adhesion and activation (17).
3. Hypothermia determines a reduction of the SECs plasma membrane (PM) fluidity. This

reduction is greater in fatty than in normal livers determining a more severe deterioration of SECs after exposure to low temperatures. Steatotic livers are therefore more prone to primary non function after OLT probably because they are more susceptible to cold preservation injury than non steatotic ones (18).

4. It has also recently been shown (19) that cold ischemia decreases liver regeneration ability after partial liver transplantation in the rat: prolonged time of cold preservation (10 and 16 hours) was, in fact, associated with a dramatic decrease of animal survivals and of all markers of regeneration (IL-6 and TNF- α).

These last two aspects represent a critical problem since new strategies to overcome organ shortage (marginal donors, cadaveric split, living related liver transplantation) are achieving an increasing importance worldwide. At the present time a great deal of efforts in clinical research is therefore focused on minimizing the ischemia-reperfusion injury that occurs to the liver graft with the current method of cold preservation. A fascinating solution, proposed by several authors, is represented by the introduction of extracorporeal circuits to preserve the liver graft with a normothermic oxygenated perfusion (20-22). These new graft preservation systems may potentially have many advantages: a better graft preservation and consequently a wider potential use of marginal and partial grafts, the possibility to assess the availability of the graft before OLT, the possibility to use non heart beating donors.

Conclusions

Thermal homeostasis is of paramount importance for both the liver recipient and the liver graft.

Hypothermia may have a catastrophic effect on coagulation and cardio-circulatory system of the liver recipient. It is essential therefore to prevent severe hypothermia during OLT with an accurate continuous temperature monitoring and with opportune external heat sources.

Thermal homeostasis is an essential component of conventional cold preservation method of the graft. Hypothermia plays at the same time a critical role in

the ischemia-reperfusion injury, however. Marginal and partial grafts, in particular, are more susceptible to the negative effects of cold preservation. New preservation strategies, such as extracorporeal circuits with normothermic oxygenated perfusion, are needed therefore to expand the donor pool without worsening OLT results.

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