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FOCUS ON: TRANSPLANTATION

Perfusates: Their properties and usage for the maintenance and storage of organs for transplantation

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SUMMARY

Organ transplantation remains the most cost-effective treatment for many patients with end-stage organ diseases. In clinical transplantation, the main concern is the continuing rise in the number of patients on transplant waiting lists and the widening imbalance between demand and supply of organs from suitable donors. In renal transplantation, the majority of kidneys available are recovered from heart beating donors (HBDs). In recent years, shortage of kidneys from these donors has led to using organs from non-heart-beating donors (NHBDs) to expand the donor pool. However, these organs are often exposed to periods of both warm and cold ischaemic damage which determine short-term and long-term functional and survival outcomes of allografts. Therefore, minimising organ responsiveness to ischaemic injury could be beneficial in improving immediate allograft function. A wide range of protocols and techniques are being developed aiming to minimise ischaemic damage and maintain organ viability between organ harvesting and transplantation. Hypothermic preservation is being used in many transplantation centres to reduce metabolic requirements and promote cellular tolerance to ischaemia. In this article, techniques used in ex-vivo organ preservation will be discussed as well as characteristics of perfusate solutions that are being used to prolong organ viability pre-transplantation.

1. Introduction

Organ transplantation has significantly improved patients lives and remains the treatment of choice for these patients with end-stage organ failure. The most commonly transplanted organs include the liver, kidney, pancreas, heart and lung. In recent years, there has been a remarkable increase in the demand of good quality kidneys for transplantation; however, the main problem affecting this field is the shortage of organs from living donors and heart beating donors (HBD), leading to increased number of patients on transplant waiting lists. Therefore, interest has turned to the use of organs recovered from marginal non-heart beating donors (NHBD) to expand the donor pool.[1]

Various factors have contributed to successful transplantation and they include: improvement in surgical techniques for implantation, better selection of donors and recipients, use of effective immunosuppressive therapies with less severe side effects, and satisfactory preservation techniques of organs recovered from cadaveric donors. The major difficulties surrounding the use of kidneys from NHBD are the inevitable periods of ischaemic damage to which these organs are subjected during harvest, storage and transplantation.[2]

However, NHBD organs are often associated with increased rates of primary non-function (PNF) and delayed graft function (DGF), which determine functional and survival outcomes of allografts. Widespread use of these organs has been limited by different reasons such as legal and logistical, ethical issues and the modern misapprehension that NHBDs are marginal donors whose organs provide poor function after transplantation.[3] Nevertheless, NHBDs are contributing to the clinical donor pool and present a largely unexploited source of organs that could have an important impact on reducing the big gap between supply and demand.[4]

2. Ischaemia reperfusion injury (IRI)

2.1. Ischaemia

In organ transplantation, IRI generated during organ harvest, storage and transplantation remains an unavoidable factor that

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contributes to immediate and long-term function of a transplanted kidney. Clinical and experimental evidence suggest that ischaemia followed by reperfusion plays a key role in the pathogenesis of early graft damage and ischaemic damage is amplified upon restoration of blood flow. It is known that kidneys obtained from NHBDs suffer varying degrees of ischaemic injury during organ procurement and storage as a result of interrupted blood flow to the organ.[5] Thus, Ischaemia is characterised by restricted blood supply to the organ leading to decreased oxygen and nutrients supply. The result is the activation of a cascade of cellular events which contribute to potentially irreversible tissue damage. Consequently, anaerobic metabolism results in a build-up of catabolites and waste products from cells and tissues, a reduction in intracellular pH and activation of lysosomal enzymes that disrupt structural cell components.

During ischaemia, adenosine triphosphate (ATP) depletion results in a rise in the concentration of hypoxanthine and in dysfunction of ATP-dependent membrane ion pumps, such as Na^+/K^+ ATPase pump, this causes K^+ ions efflux from the intracellular compartment followed by influx of Na^+ ions from the extracellular environment into the cell with subsequent water movement into the intracellular space, resulting in oedema or cell swelling.[6]

2.2. Reperfusion injury (IRI)

It was thought that reoxygenation of a previously ischaemic tissue would reduce the damage. However, restoration of blood leads to the activation of various events that contribute to a much more pronounced tissue injury known as reperfusion injury.[7] Although the pathophysiological mechanisms that lead to this damage are not full understood, IR injury remains a well-documented phenomenon.[8] Reperfusion intensifies the damage by triggering an inflammatory reaction characterised by leukocyte infiltration into the allograft, production of reactive oxygen species, activation of endothelial cells, increased expression of adhesion molecules that facilitate interactions between leukocytes and the endothelium. For example, changes that occur as consequence of renal IR injury include reduced renal blood flow, increased vascular resistance, decreased glomerular filtration rate and tubular obstruction due to erythrocyte trapping. At the renal level, IR injury is characterised by two main features: apoptosis of tubular epithelial cells and the development of interstitial inflammation.[9]

3. Methods used in organ preservation

Kidneys recovered from cadaveric NHBD are subjected to varying degree of both warm and cold ischaemic injury during organ procurement and storage prior to transplantation. Damage can be due to prolonged lack of oxygen and sufficient energy production to sustain cellular metabolic reactions. Transplantation of these kidneys is often associated with acute tubular necrosis (ATN), which leads to increased rates of delayed graft function (DGF) and poor outcome after transplantation.[10] Although various studies suggest that kidneys from NHBD show good long-term function and survival rates similar to those from HBD,[3,11] Koo et al.[7] have reported that DGF could affect short-and long-term graft survival. Therefore, attempts to minimise organ responsiveness to ischaemic damage could be beneficial in improving immediate graft function by reducing incidence of DGF.[12]

Following organ retrieval from the donor, there is requirement for effective ex-vivo preservation to limit the damaging effects of ischaemic injury and maintain viability of the organ before implantation. Over the last few decades, there has been remarkable progress in preservation techniques and the most commonly used method of organ preservation are simple or static cold storage (CS) and hypothermic machine perfusion or pulsatile machine preservation.[13] The objectives of hypothermic organ preservation consist in lowering the metabolic rate, conserving ATP stores and preventing formation of oxygen-free radicals upon reperfusion. It is important to keep the period of cold ischaemia as short as possible especially in marginal donor organ because the longer the period of cold storage the greater the risk of developing reperfusion injury.[14,15]

3.1. Hypothermic static cold storage

Hypothermic static cold storage (CS) has been clinically used since the late 1960s and is the current gold standard in the preservation of abdominal organs minimising ATP depletion and reducing cellular metabolism.[16] Experimental studies have showed that CS reduces progression of warm ischaemic injury. In CS, cold preservation solution (4–8 °C) is used to flush the blood out allowing cooling of the organ. After dissection, the organ is placed in sterile containers containing chilled preservation solution and placed on ice to allow shipping at transplantation centre.[17,18] Although, CS preservation ameliorates ischaemic damage, prolonged storage can be detrimental to the organ as it triggers a cascade of events such as oxygen depletion and accumulation of end products of metabolism from damaged cells as well as activation of catabolic enzymes, leading to irreversible injury. In addition, deterioration of cellular components and structures as well as changes in biochemical cellular functions have been observed in liver stored by CS.[19] Nevertheless, these processes are delayed by the hypothermia which decreases the rate of metabolism.[12,20] Although, CS shows the advantages of being simple, cost-effective and reproducible,[11] various studies have reported that DFG was observed in Maastricht category III and IV graft.[21] Therefore; limitations of static CS in preserving marginal organ have led to the increased use of hypothermic machine perfusion (MP).

3.2. Hypothermic machine perfusion

In recent years, numerous reports have demonstrated that hypothermic machine perfusion (MP) could preserve organs for longer periods (more than 30 h). Continuous circulation also allows assessment tests to be performed and maintain the quality of the organ until transplantation takes place.[22,23] The reports by Baicu et al.[1] and Wight et al.[10] demonstrated the superiority of MP to CS in terms of improving immediate graft function.[24] Therefore, the use of MP is contributing to extending storage time and allows pre-transplant viability assessment tests to be performed reducing the number of kidneys that would otherwise be discarded.[25] The major indicators of viable organs include vascular resistance, perfusate pressure and flow rate. Additionally, a number of biochemical parameters and markers of IR injury such as lactate dehydrogenase (LDH), glutathione S-transferase (GST) and fatty acid binding proteins (FABP) are able to be measured in the perfusates samples collected during MP also providing an indication of viability.[26] Their consideration and reliability as good indicators of kidney function is still controversial in many centres.

4. Solutions used in organ preservation

In either CS or MP, cold preservation solutions are commonly used in *ex-vivo* to minimise the damaging effects of warm ischaemia and maintain organ viability pre-transplantation.[27] The type of preservation used will determine the quality of the organ and the preference of preservation solutions varies between transplant centres.[17] Pharmacological modulation during preservation may also result in optimisation of perfusion parameters.[22] Increasingly standard preservation solutions are being supplemented with