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# Normothermic perfusion – a mini-review

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## Abstract

The quality of organ preservation is critical to the outcome of transplantation: preservation technology is a limiting factor in the further development in the use of marginal donor organs. Normothermic preservation (preservation at normal physiological temperature) enables prolonged preservation, resuscitation after warm ischaemia and organ viability assessment prior to transplantation.

### Keywords

Normothermic perfusion; Organ preservation

It is widely recognised that preservation injury is an important factor not only in the short-term but also the long-term outcome of transplantation and that success rates are directly related to the duration of cold ischaemia. In recent years, the increasing discrepancy between transplant waiting lists and the supply of cadaveric donor organs has led to the transplantation of increasingly marginal organs. This group is characterised by particularly poor tolerance of the various injuries that occur during the process of preservation and transplantation.

Although cooling reduces the metabolic rate of biological tissue, this is not halted even at (melting) ice temperature (cellular metabolism is reduced by a factor of 10 to 12-fold) and continued cellular processes lead to depletion of ATP and accumulation of metabolic products. When the organ is rewarmed and reperfused with oxygenated blood, the rapid metabolism of metabolic products within an organ depleted of energy stores leads to the complex cascade of events known as ischaemia-reperfusion, causing cellular injury via lipid peroxidation and other pathways. Much is now known about this process (1), but the principles of cold preservation (predominantly directed to the prevention of cellular swelling) have remained largely unchanged for two decades.

The use of marginal donor organs and, particularly, those from donors after cardiac death, exacerbates the problems of preservation and ischaemia-reperfusion injury, because preservation takes place on an existing background of cellular injury and energy depletion. This is a limiting factor in the use of such donor organs. The use of hypothermic machine perfusion has been shown to improve the immediate function rate of stored kidneys, but does

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not enable normal cellular metabolic function or prevent depletion of energy stores, nor does it prevent all the deleterious direct effects of cooling (2). Cold preservation, having served the needs of transplantation well for many years, is now widely seen as an important limiting factor in the further expansion of transplantation.

The principle of normothermic perfusion is to recreate the physiological environment by maintaining normal temperature and providing the essential substrates for cellular metabolism, oxygen and nutrition. Normothermic perfusion circuits generally comprise components developed for cardiopulmonary bypass. Oxygen carriage is achieved by using either whole blood (3,4), pyridoxylated bovine haemoglobin (2) or a combination of preservation solution and purified red blood cells (5). Other critical components of the perfusate include nutrition (glucose, insulin, amino acids), drugs to prevent thrombosis or micro-circulatory failure (heparin, prostacycline) and other agents to reduce cellular oedema, cholestasis and free radical injury. In addition to a reduction in ischaemia-reperfusion injury, a further potential advantage of normothermic perfusion is the assessment of viability: because the organ is metabolically active, it is possible to measure function, in order to predict post-transplant outcome before subjecting the patient to surgery. This is an increasingly important issue as more marginal organs are used.

Experimentally, normothermic perfusion has been studied in the heart (6), kidney (2), liver (4,7,8) and lung (5). In a non-transplant setting, stable metabolic, synthetic and haemodynamic function of the porcine liver has been reported for up to 72 hours (3). Normothermic perfusion enables successful transplantation of organs following ischaemic damage that would be incompatible with cold preservation – 120 minutes warm ischaemia of the canine kidney (2), 60 minutes warm ischaemia of the porcine liver (this system included a dialysis device) (4), and 65 minutes warm ischaemia in porcine lung transplantation (5). The emphasis in experimental studies published to date has been on the preservation of organs with warm ischaemic injury; the challenge of prolonging the duration of preservation has been complicated by the technological problems in maintaining artificial blood circuits beyond 24 hours although, most recently, successful transplantation of the porcine liver has been achieved after 40 minutes warm ischaemia and 20 hours preservation (8)..

To date the only uses of normothermic perfusion in a clinical environment have been in heart and lung transplantation. Approximately 80 clinical heart transplants have been carried out worldwide using the ‘Organ Care System’ developed by the Transmedics company, which has been shown to be safe and effective: it also permits ex-vivo donor heart assessment including identification of occult pathology such as donor coronary disease (personal communication S Tsui). Steen et al. reported five clinical double lung transplants with lungs from brain-dead donors which had been declined on conventional criteria, mainly due to low arterial oxygen tensions. It proved possible to recondition these lungs during the course of 1 to 2 hours of ex vivo perfusion after which the lungs were kept on extra-corporal membrane oxygenation (ECMO) at 8°C until transplantation the next day. The time from retrieval until the start of reperfusion of the transplanted lung was approximately 20 hours in all cases. Although the use of ex-vivo perfusion may not be the sole reason for success, nonetheless, the postoperative course was uncomplicated with an observation period of 3 to 6 months (9).

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As the utility and potential benefits of normothermic preservation are more widely recognised, we may expect to see further clinical trials in other areas of transplantation. This technology will come at a price in terms of complexity and financial cost and it is likely that such developments will only become commercially viable if it can be proven that such technology does enable successful transplantation of organs that could not otherwise be transplanted. Clinical trials will, therefore, need to include such high-risk donor organs, further complicating ethical and other aspects of trial design. Also, before this technology can be widely used, considerable development will be needed to ensure that it is both portable and reliable.

Normothermic perfusion may be complementary to other strategies for organ resuscitation, including normothermic recirculation (attachment of the donor to cardiopulmonary bypass immediately after death prior to retrieval of organs) (10). Additional benefits may include the use of therapeutic gene therapy in transplantation: normothermic perfusion may provide an ideal environment for the local gene delivery, perhaps to further protect against ischaemia-reperfusion injury (11) or reduce the risk of rejection by immunomodulation (12) and a wide range of other potential applications.

It is likely that static cold preservation has reached the end of its development potential and that the future of organ preservation lies in providing an optimised physiological environment to enable organ assessment, resuscitation and modulation. Normothermic perfusion is inherently complex, but experimental and early clinical results suggest that this technology may prove to be a significant step in the evolution of organ transplantation.

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