Medical research

Improved organ recovery after oxygen deprivation

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A modified method for delivering oxygen to the whole body can restore function in pig organs one hour after the animals have died. The achievement points to ways to improve transplants and the treatment of strokes and heart attacks. See p.405

Without oxygen, mammalian cells die. Paradoxically, restoring oxygen to cells that have been deprived of it also causes stress and damage – a phenomenon called reperfusion or reoxygenation injury[1]. For decades, scientists have been searching for strategies to protect cells and organs against the detrimental effects of oxygen deprivation and reintroduction that can occur following stroke, heart attack or the cessation of breathing. On page 405, Andrijevic *et al.*[2] describe a system called OrganEx that enables oxygen to be recirculated throughout a pig's body, preserving cells and organs an hour after a cardiac arrest.

The group that performed the current study had previously developed a technique called BrainEx to restore some degree of metabolic activity in the cells of pig brains after up to six hours of oxygen deprivation[3]. The strategy involved a specialized fluid called a cryoprotective perfusate, which was pumped through the brain's blood vessels (this passage of fluid through vessels is known as perfusion). The perfusate consisted mainly of a liquid containing Hemopure – a synthetic form of the protein haemoglobin, which carries oxygen in red blood cells. The perfusate also contained a wealth of molecules that help to protect cells (cryoprotective agents) and prevent blood clots.

In the current study, Andrijevic *et al.* optimized this perfusate for whole-body reperfusion, altering the cryoprotective agents and antibiotics it contained, among other changes. They pumped their perfusate through the body using a computer-controlled system that involved a perfusion pump, an oxygenator and a haemodialysis unit, which maintains stable levels of electrolytes and other essential molecules in the perfusate.

The authors compared OrganEx with a more-conventional heart-and-lung substitution device – an extracorporeal membrane oxygenation system (ECMO), which pumped the pig's own blood, carrying fresh oxygen, through its body. They induced cardiac arrest in the pigs, and left them for one hour after death. They then performed whole-body recirculation and reoxygenation for six hours. The ECMO failed to lead to proper perfusion of all organs, and the authors found that many smaller blood vessels had collapsed (Fig. 1). By contrast, use of the OrganEx system resulted in full reperfusion and stable oxygen consumption, and the authors did not detect the electrolyte disturbances and abnormally acidic body fluids typical of oxygen deprivation. In-depth analyses of brain, heart, lung, liver, kidney and pancreas tissues revealed less cellular destruction and more evidence that cell repair was being promoted following OrganEx perfusion than with ECMO. For example, the investigators found more evidence of cell proliferation in the kidneys of OrganEx-perfused pigs.

Andrijevic and colleagues went on to provide insights into the mechanisms by which cell injury and death occur following oxygen deprivation. The group performed single-cell analysis of gene expression in the animals' kidney, liver and heart. This revealed substantial differences between the OrganEx and ECMO animals in the expression of genes involved in various functions, including cell death and inflammation.

This comprehensive and well-designed study has the potential to lead to new treatment strategies for people who have a heart attack or stroke. One could imagine that the OrganEx system (or components thereof) might be used to treat such people in an emergency. Of note, though, more research will first be needed to confirm the safety of the system's components in specific clinical situations.

However, the main benefit of OrganEx might be for certain types of organ donation. Organ donation after death can be split into two categories: donation after circulatory death (DCD) and donation after brain death (DBD). Individuals who become DBD donors lack brain stem function but have intact blood circulation. By contrast, individuals who become DCD donors have severe, irreversible brain injury, with further treatment unlikely to result in recovery, and they are relying on respiratory and circulatory support for survival[4]. Organs retrieved from individuals following circulatory death, after support systems have been switched off, are damaged owing to the intervening period of warm-oxygen deprivation. As a result, organ transplant following DCD is associated with worse outcomes than with DBD.

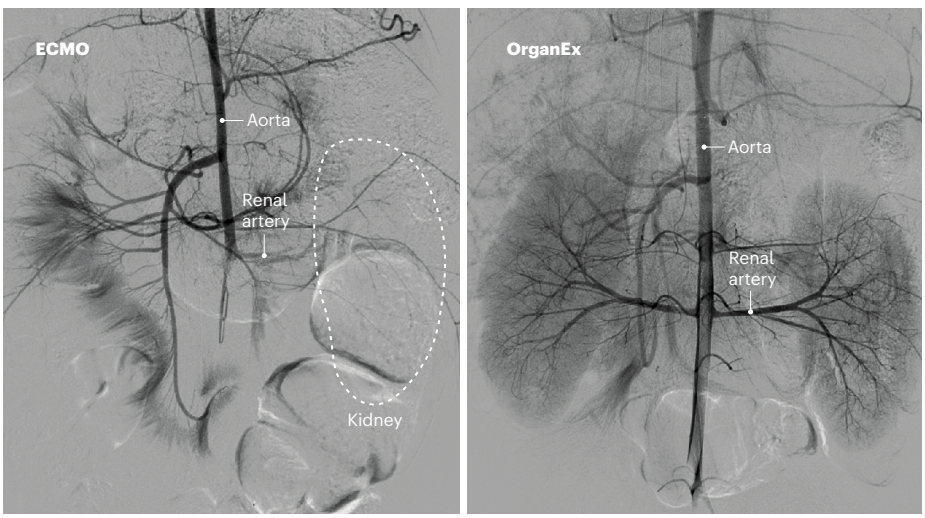

Figure 1 | Reperfusion of pig kidneys after cardiac arrest. Oxygen deprivation, for example following a heart attack, can cause lasting tissue damage. During severe circulatory or respiratory failure, a heart-and-lung substitute called an extracorporeal membrane oxygenation system (ECMO) is conventionally used to pump oxygenated blood round the body (reperfusion) to restore tissue function. Andrijevic *et al.*[2] developed a system called OrganEx that uses a specialized fluid and computer-based monitoring system for whole-body reperfusion. They compared the effectiveness of ECMO and OrganEx in pigs that had been subjected to a cardiac arrest and left for an hour. OrganEx produced substantially better reperfusion than did ECMO. Reperfusion is seen here in the kidneys; black indicates where fluid has reperfused. (Figure taken from Fig. 2a of ref. 2.)

The conventional method for protecting organs derived from both DBD and DCD donors between procurement and implantation involves rapid cooling and static storage in an ice-cold preservation fluid. This substantially reduces the organ's metabolism and oxygen requirements – but does not completely eliminate them[5]. This fact, coupled with a global donor shortage that makes it necessary to use donor organs of lower than optimal quality (which have a reduced tolerance to oxygen deprivation), has led to increased interest in preservation methods involving oxygenated machine perfusion. This can be performed either *in situ* in the donor or *ex situ* for isolated organs[6,7]. Increasingly, abdominal perfusion using an ECMO-like device is being used to allow reoxygenation and resuscitation of organs derived from DCD donors before procurement and static cold storage[4], with methods applied to avoid unwanted recirculation of oxygen to the severely injured brain. Andrijevic and colleagues' work indicates that this strategy could be improved and refined by the OrganEx system. In a situation involving a DCD donor, one would have to prevent reperfusion of the brain, for example by using a balloon catheter to block the thoracic aorta or by clamping the cerebral blood vessels[4].

The OrganEx system uses some components that are already used in *ex situ* machine perfusion of donor organs[8], such as antioxidants and Hemopure, alongside several innovations. Because the investigators used a multimodal approach to test this multifaceted system, it remains to be determined whether all of its components contribute to the benefits they observed. One advantage over ECMO might arise from the use of Hemopure, which has a small molecular size compared with that of red blood cells, allowing oxygen delivery through tiny collapsed vessels[9]. Another might come from the fact that Andrijevic and colleagues' perfusate contained pharmacological inhibitors of cell death. Finally, inclusion of a haemodialysis unit has already proved beneficial in the prolonged *ex situ* machine perfusion of isolated livers[10]. It therefore stands to reason that it might also improve *in situ* machine perfusion in DCD donors.

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1. Wu, M.-Y. *et al. Cell Physiol. Biochem.* **46**, 1650–1667 (2018).
2. Andrijevic, D. *et al. Nature* **608**, 405–412 (2022).
3. Vrselja, Z. *et al. Nature* **568**, 336–343 (2019).
4. Domínguez-Gil, B. *et al. Intensive Care Med.* **47**, 265–281 (2021).
5. Jing, L., Yao, L., Zhao, M., Peng, L. & Liu, M. *Acta Pharmacol. Sin.* **39**, 845–857 (2018).
6. O'Neill, S. & Oniscu, G. C. *Curr. Opin. Organ Transplant.* **25**, 59–65 (2020).
7. van Rijn, R. *et al. N. Engl. J. Med.* **384**, 1391–1401 (2021).
8. Matton, A. P. M. *et al. Liver Transplant.* **24**, 528–538 (2018).
9. Davis, J. M. *et al. Transfusion* **58**, 132–137 (2018).
10. Lascaris, B. *et al. Am. J. Physiol. Gastrointest. Liver Physiol.* **322**, G183–G200 (2022).

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