# Comment

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A transplant surgeon in Berlin prepares organs donated by a woman with brain death.

# Partially revived pig organs could force a rethink of critical-care processes

**Brendan Parent**

Procedures used in life support and to preserve organs in deceased human donors might one day need to be re-evaluated in the wake of a study that restored some cell function in pigs one hour after death.

In 2019, neuroscientists and other researchers used a network of pumps, heaters and filters to control the contents, flow and temperature of a solution in the brains of pigs. Remarkably, the perfusion system, called BrainEx, was able to restore certain structural and functional properties in the pigs' brains — even though the animals had been decapitated for food production four hours before[1].

Now, in this week's *Nature*, a team at the Yale School of Medicine in New Haven, Connecticut, led by the developers of BrainEx, present an update to their system[2]. OrganEx restored circulation and repaired damaged cells throughout the bodies of pigs that had been dead for one hour.

Currently, a perfusion technique called extracorporeal membrane oxygenation (ECMO) is used in hospital settings to support patients whose heart, lungs or both have ceased to function. The Yale team showed that, after six hours of perfusion, OrganEx did much better than ECMO in terms of getting fluids flowing again in arteries and organs. And whereas ECMO only slows cell death, OrganEx greatly improved the cellular architecture in tissues, including in the brain. It even activated genetic programmes involved in cellular repair and restoration of normal cell

function in the pigs' kidneys, hearts and livers[2].

Today, ECMO is deployed mainly as a life-saving intervention for patients with severe heart and lung conditions, but there has been growing interest in using it to preserve organs in people for whom resuscitation has failed. Major advances in perfusion technologies could some day increase the likelihood of physicians being able to resuscitate patients, as commentators noted in 2019 (ref. 3). That potential could also make it harder for surgeons to ethically justify the use of perfusion to recover transplantable organs after patients' hearts or lungs have stopped working.

The latest findings raise a slew of questions — not least, whether medical and biological determinations of death will need revising. To be better prepared for that possibility, physicians might need to rethink how they are using perfusion systems. Here, I describe current practice. I also lay out what needs to be done differently — both to improve care now, and to ensure that future technologies are used to patients' benefit, not detriment.

ZIV KOREN/POLARIS/EYEVINE

A person with severe COVID-19 in Israel is treated using an ECMO heart–lung machine.

## Perfusion process

When a patient's heart or lungs — or multiple organs — have stopped working, clinicians might deploy heart-shock therapy, medications such as blood thinners or machines that sustain blood flow and oxygenation.

Increasingly, ECMO is one of the treatments physicians use in this scenario. The technique uses the patient's own blood, or in some cases blood from a donor, to mitigate organ damage caused by a lack of oxygenation and blood flow.

First used to treat a patient with acute respiratory failure in the early 1970s, ECMO is now used by at least 543 centres worldwide, including every major teaching hospital in the United States (see 'Perfusion in people'). Over the past three decades, more than 95,000 patients globally (many of whom had experienced heart attacks, heart inflammation or hypothermia) have been discharged from hospital after being treated with ECMO and a technique called extracorporeal cardiopulmonary resuscitation (ECPR). And many have been able to resume at least some activities of daily life.

Where the use of ECMO becomes more ethically fraught is in the preservation of organs in people who have died.

Most organ donation takes place after irreversible loss of all brain function (known as brain death). But each year, many more people are declared dead on the basis of irreversible loss of circulatory and respiratory function — called cardiorespiratory death. For instance, in US hospitals in 2012–16, there was one brain death for every 50 cardiorespiratory deaths[4]. There is therefore growing interest in the use of ECMO in a process called normothermic regional perfusion (NRP), which preserves the organs of donors who have been declared dead on the basis of cardiorespiratory criteria.

> **"How might OrganEx, or something like it, affect how these technologies can be used?"**

Under what circumstances might NRP be deployed today? If a patient's condition fails to improve, at a certain point, carers might deem continued treatment to be 'medically futile'. In legal and policy documents, medical futility generally means that care no longer has a reasonable chance of extending or improving life[5]. But people differ in their judgement about when that point is reached (even within the same institution), depending on their value system, medical goals and personal biases. For instance, estimations varied widely in three studies (conducted in separate countries) in which physicians were asked to predict the likelihood of a patient surviving cardiac arrest in various cases[6–8].

Once medical futility is determined, however, death is allowed to proceed — as long as the family members and clinical team agree to withdraw or withhold life-sustaining treatment. If the patient is declared dead on the basis of cardiorespiratory criteria, treatment such as ECMO is removed, or defibrillation shock treatment is stopped. The heartbeat stops, and all circulation and oxygenation to the tissues ceases.

At this point, nothing is done for a 'stand-off period' of between 2 and 20 minutes[9]. Then, if organ donation had been previously authorized, NRP can be deployed. This might mean restarting ECMO if it had already been used as a life-saving intervention. If organs are being recovered from the thorax, the patient's cerebral arteries are blocked to stop blood flow to the brain. This is done to prevent any possibility that the person who has died might regain any capacity for experience as a result of the perfusion.

Currently, there is no central registry collecting data on the use of NRP. But reports from transplant centres around the world indicate that this technique has so far been used to preserve several hundred organs globally.

In principle, NRP could help to supply high-quality organs to the millions of people worldwide who are waiting for transplants. In the United States, one estimate suggests that the pool of donors could be increased by 20%

if surgeons were able to recover transferable hearts from those who are declared dead on the basis of cardiorespiratory criteria[10].

Some ethicists and physicians have argued that the process of blocking arteries in NRP undermines the original declaration of death — and that another approach, called *ex situ* preservation, in which the organs are extracted from the body before being perfused, is less ethically fraught[11]. Others (myself included) counter that, in cases where NRP has been used, the initial choice to withdraw care depended on a clinically grounded decision that death should be allowed to proceed, as well as the observation that, when care was withdrawn, the heart was unable to beat on its own[12,13].

Currently, the same technology is used in both ECPR and NRP. That might cause some to question whether ECMO could ever be ethically used in NRP without first being used to try to save the patient's life during ECPR. But studies show that, although ECMO can promote some cellular recovery in isolated organs, it has limited capacity to restore an entire human body, even after just a few minutes of no blood flow[2]. Given this, in my view, the use of NRP without ECPR can be ethically justified — as long as the cause of death, the amount of time during which there has been no blood flow, and other factors indicate that ECPR will be futile.

## Technology trials

How might OrganEx, or something like it, affect how these technologies can be used?

There are clearly cases in which ECMO is unable to restore a patient's consciousness or a spontaneous heartbeat. But ECMO can restore the deceased's organs for transplant. Were a future iteration of OrganEx ever to be used in humans, there might be few cases where it could restore organs without also restoring some important level of brain and heart function.

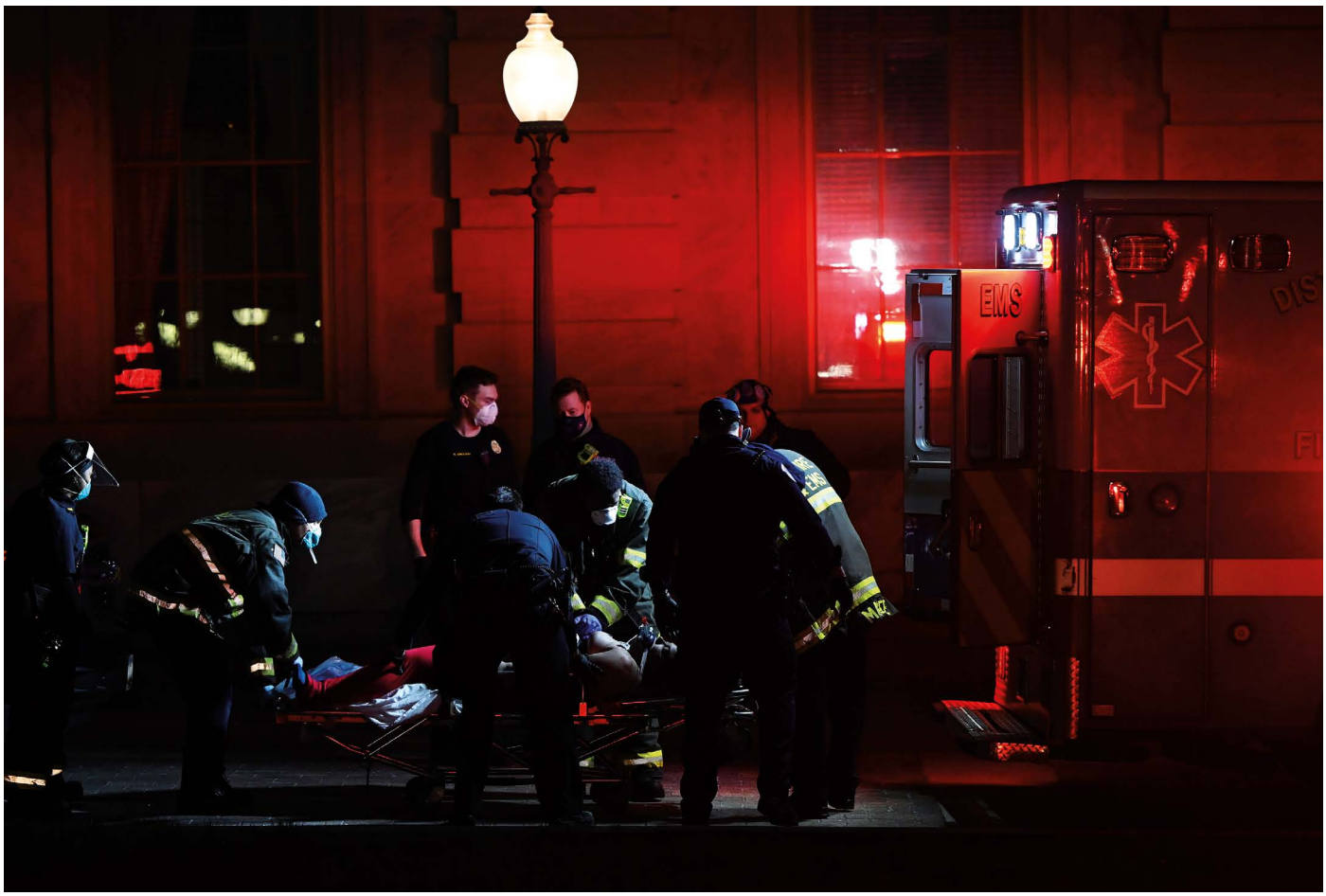
The capacity to initiate cellular repair across all organs, including the brain, might mean such a technology would have to be trialled for much longer — or after a much longer period without blood flow — before medical futility could be determined. By then, so much organ damage might have occurred that the patient's organs would no longer be transplantable.

It is also possible that a future iteration of OrganEx could increase the risk that people who have been resuscitated are then unable to get off life support. This situation is known in medical communities as the 'bridge to nowhere', and has already become more common with increased use of ECMO in ECPR[14].

In my view, three changes to current practice would improve care today — and better prepare hospitals and patients for the range of ethically fraught scenarios that might emerge from advances in perfusion technology.

**Better data.** For several decades until the early 2000s, various clinicians and researchers tried to review the criteria used to determine medical futility — with the aim of creating more-quantitative standards for physicians[15]. Such studies created reliable methods for predicting whether homogeneous groups of patients would survive or die under certain circumstances. But predictions based on cohorts don't seem to have extrapolated to individuals[15]. Today, the use of powerful analytical methods, such as machine-learning algorithms that examine data sets from hundreds of thousands of patients, could help.

In relation to the use of ECPR, data are lacking on which patient characteristics are tied to particular outcomes. This is partly because ECMO programmes, which require expensive machines and trained personnel, are still not widespread. Some patients who are given ECPR will be discharged from hospital. In other cases, the care team will determine medical




ANDREW CABALLERO-REYNOLDS/AFP/GETTY

**Paramedics in Washington DC perform cardiopulmonary resuscitation on a patient.**

futility. In yet others, the patient or their family members will have to make an excruciating decision about whether life support should be withdrawn, even if ECPR had returned the patient to consciousness.

Knowing the clinical conditions under which ECPR should or should not be used is key to ensuring that the technology benefits rather than harms patients. Such data would also help physicians to know when perfusion could be used ethically for organ recovery.

A promising start in this regard is the Extracorporeal Life Support Organization (ELSO) Directory, a non-profit registry that is collecting data from more than 60 countries on the use of ECMO as a life-saving intervention (see go.nature.com/3przrhx). But participants should also be encouraged to submit data for cases in which carers decided not to use ECPR, and follow-up data on survivors who were discharged from hospital. Analysts, with the help of machine-learning models, also need to look for more-nuanced correlations.

If ECMO researchers and funders committed to a substantial effort to collect relevant big data, two types of organization could take the lead on appraising that research and guiding the use of perfusion technologies. These are critical-care associations, such as the Society of Critical Care Medicine in Mount Prospect, Illinois, and professional transplant associations, such as the European Society for Organ Transplantation in Padua, Italy.

Ideally, such bodies would work collaboratively with medical ethicists to assess whether current clinical practice is ethical, and how best to study new technologies such as OrganEx. They could also evaluate whether new perfusion methods are ready for clinical use.

**Better communication.** Even if better data are obtained to support physicians' decisions to withdraw or sustain life support, determinations of medical futility should not be made on the basis of clinical data alone. Prospective patients must be able to direct their own course of care, as well as decide what happens to their bodies after they die.

Currently, communication between physicians, lawyers, patients and family members regarding goals for end-of-life care, and for organ and tissue donation after death, is inconsistent at best. By 2016, for example, only about one in three people in the United States had any form of advance directive such as a living will[16]. And often, as one US study noted, a person's socioeconomic status can influence whether they have access to doctors and lawyers for conversations and information about advance care planning[17].

Based on protocols I've read and conversations I've had with US clinical teams, it seems that ECPR is rarely, if ever, brought up during discussions about treatment preferences at the end of life. Also, few people are likely to know about techniques such as NRP, let alone consider its implications, when deciding whether to be organ donors.

Likewise, when families of people who have died are approached by organ-procurement organizations to authorize donation – during which NRP will be used – communication seems to be highly varied across institutions. Most families of potential donors, and most organ recipients, are not told during consent processes that the clinical team will be blocking blood flow to the brain of the deceased, or that the same technology that makes donation possible is sometimes used to try to save lives. It is also unclear how much of this information people should be told, particularly given the stress they might already be under.

What donor families and organ recipients want to know – and what they should know – must be better studied and better understood by ethicists, social workers, psychologists and others involved in transplant medicine. Conversations about the various scenarios that can follow a heart attack or respiratory failure, say, should take place much earlier than they do today – perhaps even in universities or schools as part of biology curricula. This is especially the case if new ECPR and organ-recovery methods become integrated into the clinic.

**Commitment to equity.** Lastly, ECMO and other perfusion technologies should be made as equitably available as possible – along with adequate personnel, training and the most current protocols.

According to one US study, the use of ECMO is highest per capita in the Northeast of the country, even though more people in the comparatively poorer South die from heart disease and acute respiratory distress syndrome[18]. And the only part of the country where mortality has increased following the implementation of ECMO in critical and emergency-care centres is the Midwest – an area that is also less well resourced than the Northeast.

Trialling and implementing OrganEx – especially as a way to facilitate the recovery of organs – will probably happen first in Europe, if it happens anywhere. In the United States, there is considerable mistrust around organ donation, especially among people of colour[19], and no more than 20 of around 250 transplant centres are attempting NRP. No US protocols currently integrate the use of ECMO for ECPR and NRP.

Yet regardless of where OrganEx in humans might one day be used, researchers, physicians and policymakers must take steps to ensure that it is not someone's postal code that determines whether they survive thanks to ECPR, or whether they become an organ donor.

No one yet has answers to the many questions raised by the latest findings from the Yale team. Re-examining how physicians are using circulation technology in the clinic today is the first step towards resolving them.

## Perfusion in people

**Over the past 50 years, use of a perfusion system called extracorporeal membrane oxygenation (ECMO) in people has steadily increased.**

The ECMO system was first used in the early 1970s to treat a patient with acute respiratory failure. It is now used routinely by more than 500 centres worldwide as a life-saving intervention in patients whose hearts, lungs or both have stopped working.

In 2018, a centre in Porto, Portugal, piloted the dual use of ECMO — as a life-saving intervention and as a way to preserve organs for donation[20]. Eight European countries now use ECMO to preserve donors' organs. Less than 8% of US organ-transplant centres do the same.

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