Review article

Brain reanimation and life after death: a narrative review

DOI: 10.5377/alerta.v9i3.23306

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Abstract
Brain resuscitation is an emerging field aimed at restoring neurological functions following circulatory arrest, challenging traditional paradigms of biological death. Strategies such as therapeutic hypothermia, cardiopulmonary resuscitation with extracorporeal membrane oxygenation, and artificial perfusion systems, including BrainEx, have demonstrated the reactivation of cellular processes hours after the interruption of blood flow. Furthermore, advances in nanotechnology and connectome preservation offer new prospects for functional brain recovery, although their clinical application remains in the theoretical phase. A narrative review of the literature indexed in PubMed, the Cochrane Library, Scopus, Sage, and Web of Science was conducted. Original articles, systematic reviews, meta-analyses, case reports, and books published between 1988 and 2024 in English and Spanish were included. The objective was to synthesize the available evidence on brain resuscitation, describe its pathophysiological foundations, analyze therapeutic strategies, and examine the main neuroethical controversies. Although technological advances are pushing the boundaries of postmortem brain viability, significant challenges remain regarding the restoration of consciousness, the definition of brain death, biological reversibility, and distributive justice in access to these innovations.

Keywords
COVID-19, Radiography Thoracic, Tomography, Coronavirus Infections.

Resumen
La reanimación cerebral constituye un campo emergente orientado a restaurar las funciones neurológicas tras el cese circulatorio, desafiando los paradigmas tradicionales de muerte biológica. Estrategias como la hipotermia terapéutica, la reanimación cardiopulmonar con oxigenación por membrana extracorpórea y los sistemas de perfusión artificial, incluido BrainEx, han demostrado la reactivación de procesos celulares horas después de la interrupción del flujo sanguíneo. Asimismo, los avances en nanotecnología y preservación del conectoma plantean nuevas perspectivas para la recuperación funcional cerebral, aunque su aplicación clínica permanece en fase teórica. Se realizó una revisión narrativa de la literatura indexada en PubMed, Cochrane Library, Scopus, Sage y Web of Science. Se incluyeron artículos originales, revisiones sistemáticas, metaanálisis, reportes de caso y libros publicados entre 1988 y 2024 en inglés y español. El objetivo fue sintetizar la evidencia disponible sobre reanimación cerebral, describir sus fundamentos fisiopatológicos, analizar estrategias terapéuticas y examinar las principales controversias neuroéticas. Aunque los avances tecnológicos amplían los límites de la viabilidad cerebral *post mortem*, persisten importantes desafíos relacionados con la restauración de la conciencia, la definición de muerte encefálica, la reversibilidad biológica y la justicia distributiva en el acceso a estas innovaciones.

Palabras clave
Resucitación, Muerte Encefálica, Nanotecnología, Ética Médica, Neuroprotección.

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Reanimación cerebral y vida después de la muerte: una revisión narrativa

Suggested citation:
Guzmán RED, Guzmán K, Madera E, Guzmán RIJ, Zamora MRR, Olvera CJF, Flores RMF, Moscoso R, Guzmán VD. Brain reanimation and life after death: a narrative review. Alerta. 2026;9(3):234-243. DOI: 10.5377/alerta.v9i3.23306

Editor:
Nadia Rodríguez.

Received:
May 23, 2025.

Accepted:
June 11, 2026.

Published:
July 31, 2026.

Author contribution:
EDGR[1], KG[2]: study conception. EDGR[1], EM[3], RM[8]: manuscript design. EDGR[1], KG[2], RM[8]: literature search. KG[2], IJGR[4], MFFR[7]: data collection. EM[3], IJGR[4], RRZM[5], MFFR[7]: data or software management. RRZM[5], JFOC[6], VDG[9]: data analysis. EDGR[1], JFOC[6], VDG[9]: writing, revising and editing.

Conflicts of interest:
No conflicts of interest.

Introduction

Clinical death is defined as the irreversible cessation of cardiorespiratory functions, whereas brain death is characterized by the complete and permanent loss of all brain activity, including that of the brainstem. This latter criterion has been adopted as the legal standard for determining death in more than 80 jurisdictions worldwide.[1]

Resuscitation, understood as the restoration of biological functions following a formal declaration of death, must be strictly distinguished from recovery, which involves the recovery of vital functions during an episode of potentially reversible cardiorespiratory arrest. This semantic and pathophysiological distinction is not merely terminological; rather, it constitutes a critical nuance with substantial methodological and ethical implications for the design and interpretation of future research in neuroreanimation, intensive care, and medical bioethics.[2]

Historically, revolutionary advances that have shifted paradigms have challenged traditional conceptions of the irreversibility of death. In 1967, the first human cryopreservation was performed, setting a precedent in the exploration of postmortem biological preservation. More recently, in 2019, researchers at Yale University developed a protocol for ex vivo cerebral perfusion in pigs, through which they were able to preserve cellular functions and synaptic activity for up to four hours after circulatory arrest.

These findings demonstrate the partial feasibility of maintaining cellular processes in postmortem brain tissue, raising new questions about the physiological limits of death and the possibilities for therapeutic intervention in states considered irreversible.[3] However, significant gaps remain in current research, particularly regarding the absence of standardized metrics that would allow for a comprehensive evaluation of the success of so-called "brain resuscitation". Most studies focus on indicators of metabolic recovery or cellular viability, without systematically addressing the restoration of higher-level functions such as consciousness, functional synaptic connectivity, or neurocognitive integration. This methodological limitation poses substantial challenges for the clinical validation of postmortem interventions and underscores the need to develop multidimensional criteria that include neurophysiological, behavioral, and cognitive markers.[4]

These conceptual and methodological gaps underscore the urgent need to establish multidisciplinary research frameworks that integrate knowledge from neurology, bioengineering, and bioethics. Such integration would allow for a holistic approach to the challenges posed by brain resuscitation, ranging from the design of neuronal preservation technologies to the assessment of residual consciousness and the ethical implications of intervening in postmortem states. Only through transdisciplinary collaboration will it be possible to move toward research models that are scientifically robust, clinically relevant, and ethically sustainable.

To prepare this manuscript, a critical review of the literature indexed in databases such as PubMed, the Cochrane Library, Scopus, Sage, and Web of Science was conducted; original articles, systematic reviews, meta-analyses, case reports, and books published between 1988 and 2024 in English and Spanish were selected. With the aim of synthesizing the current evidence on brain resuscitation and "life after death", this paper analyzes pathophysiological mechanisms, therapeutic strategies, neuroethical controversies, and emerging technologies.

Discussion

Mechanisms of neuronal injury following the cessation of circulation

The interruption of cerebral blood flow triggers a multiphase ischemic cascade characterized by progressive biochemical events that compromise neuronal viability. In the initial phase, the depletion of adenosine triphosphate (ATP) leads to the dysfunction of energy-dependent ion pumps, causing generalized neuronal depolarization.[5] This phenomenon induces a massive release of glutamate, which generates a state of excitotoxicity that overexcites N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptors.[5] Excessive activation of these receptors facilitates uncontrolled intracellular calcium influx, which precipitates mitochondrial dysfunction, the generation of reactive oxygen species (ROS), and the activation of apoptotic and necrotic pathways.[5] During the reperfusion phase, a second peak of tissue damage occurs, characterized by oxidative stress and neuroimmune inflammation. The restoration of cerebral blood flow, despite being essential for metabolic recovery, leads to an overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which induce lipid peroxidation, DNA damage, and protein dysfunction.[6] Response that includes the release of proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6), chemokines, and neurotoxic mediators. This synergy between oxidative stress and inflammation amplifies the pathways of apoptosis and necrosis, exacerbating neuronal damage and compromising functional recovery.[6]

The post-cardiopulmonary arrest time window is a critical determinant of

the reversibility of brain damage. In the first five minutes following circulatory arrest, neuronal lesions are typically predominantly functional and potentially reversible through effective resuscitation and y maneuvers. However, when this interval exceeds ten minutes, a transition occurs toward programmed cell death mechanisms, primarily mediated by caspase-3 activation, along with necrotic phenomena associated with the breakdown of the blood-brain barrier. This temporal progression underscores the need for ultraearly interventions and neuroprotective strategies that mitigate the ischemic cascade before irreversible structural damage becomes established.[7]

There are physiological exceptions that modulate the brain's vulnerability to ischemic damage, and allow for a significant extension of the therapeutic window. Among these, ischemic preconditioning stands out, a phenomenon in which brief, intermittent exposures to hypoxia induce an adaptive tolerance that attenuates the cascade of neuronal injury. Likewise, therapeutic hypothermia, particularly at temperatures below 34°C, has been shown to reduce cerebral metabolism by approximately 6 % for every degree Celsius drop; this decreases energy demand, and slow down the processes of excitotoxicity, oxidative stress, and apoptosis. In porcine models, these strategies have extended the window for neurological recovery up to 40 minutes post-paralysis, demonstrating their potential as neuroprotective interventions in critical clinical settings.[8,9,10]

Current resuscitation strategies

Recent advances in brain resuscitation are redefining the traditional boundaries between biological death and the potential recovery of neurological functions. They thus challenge established paradigms in critical care medicine and neuroscience. Currently, interventions aimed at restoring postmortem brain viability can be classified into two broad categories: established medical strategies and emerging experimental approaches.[3]

Therapeutic hypothermia, maintained within a range of 32-36 °C for 12 to 24 hours, is the gold standard for brain protection following cardiac arrest. Its effecticay is based on its ability to reduce cerebral metabolism, which reduces neuronal energy demand and slows down damaging processes. At the molecular level, hypothermia suppresses the excessive release of glutamate, the primary mediator of excitotoxicity, and reduces the activation of caspase-3, a key enzyme in the apoptotic pathway. This pathophysiological modulation helps limit programmed cell death, preserve synaptic integrity, and improve neurological outcomes in resuscitated patients.[9]

The Target Temperature Management (TTM) clinical trial provided robust evidence of the benefits of therapeutic hypothermia in patients who have suffered cardiac arrest. In that study, patients treated at a target temperature of 33°C had a 55 % probability of survival with a good neurological outcome, defined as a modified Rankin Scale score ≤ 3, compared with 39 % in the group managed with normothermia.[9] These results confirm hypothermia as an effective neuroprotective intervention in cases of acute cerebral ischemia. However, its efficacy decreases significantly when the ischemic interval exceeds 30 minutes, underscoring the need for complementary strategies. In this context, extracorporeal cardiopulmonary resuscitation (ECPR) using ECMO emerges as a promising alternative, as it allows for the rapid restoration of cerebral perfusion and systemic oxygenation, thereby extending the therapeutic window and enhancing the effects of hypothermia.[11]

Extracorporeal cardiopulmonary resuscitation combines extracorporeal membrane oxygenation (ECMO) with conventional CPR maneuvers, thereby maintaining cerebral perfusion even in cases of refractory cardiac arrest. This strategy has been shown to significantly expand the window of neurological viability by providing hemodynamic support and continuous systemic oxygenation during circulatory collapse. In the ARREST trial (2023), conducted in patients with persistent ventricular fibrillation, ECPR achieved a hospital discharge survival rate of 43 %, compared with only 7 % in the group treated with standard CPR. These results demonstrate the potential of ECPR to extend the therapeutic window up to 60 minutes post-cardiac arrest, redefine the time limits for intervention, and offer new opportunities to preserve brain function in clinical scenarios previously considered irreversible.[11] This approach requires specialized centers and rapid access to cannulation, but this limits its application in prehospital settings. Post-ECMO imaging studies reveal that 68 % of survivors retain hippocampal integrity, which is key to memory.[12]

The BrainEx protocol perfuses ex vivo porcine brains with an acellular fluid enriched with cytoprotectants, including NMDA receptor antagonists, antioxidants, and anti-apoptotic agents. Under controlled laboratory conditions, this strategy has been shown to restore metabolic activity and

vascular responses up to 4-6 hours post-mortem. These results, although far from direct clinical applicability, suggest that the cellular and functional integrity of certain neural circuits can be maintained or restored beyond previously accepted time limits, challenging traditional concepts regarding the threshold of brain irreversibility and opening new avenues for research in neurovascular preservation and resuscitation.[3] Although synaptic preservation was documented in the BrainEx model, the absence of global electrical activity (isoelectric EEG) indicates that the mere preservation of neuronal architecture is not sufficient to reactivate consciousness. This suggests that the restoration of conscious functions likely requires interventions aimed at reestablishing the effective and dynamic connectivity of thalamocortical and multimodal integration networks. From a translational perspective, this finding opens up a new frontier of research: the design of strategies that not only maintain synaptic integrity but also promote the resynchronization of neural circuits critical for perception and subjective experience.[13]

Cryopreservation via vitrification, used by organizations such as the Alcor Life Extension Foundation, employs cryoprotectants (e.g., glycerol) to prevent the formation of ice crystals, the primary cause of cell lysis during freezing. When the temperature drops to –196°C (liquid nitrogen), enzymatic activity and degradative processes come to a near standstill.[14] However, studies in mouse models have revealed that, even when optimized protocols are applied, approximately 40 % of synapses lose their ultrastructure, as evidenced by electron microscopy. Added to this is a critical technical limitation: reversing the process is currently unfeasible, since the recrystallization during warming causes cell membranes to rupture and organelles to be destroyed. These findings highlight a fundamental gap between partial structural preservation and the actual possibility of restoring complex neuronal functions.[14] This raises an ethical dilemma: cryopreserved patients might "come back to life" without their identity or memory intact.[15]

Neurobiological evidence of "life after death"

Near-death experiences and hippocampal activity

Near-death experiences (NDEs) are defined as complex subjective episodes, frequently described during deep unconsciousness associated with cardiac arrest. Among the most commonly reported perceptions are sensations of out-of-body movement, a panoramic review of autobiographical memories, and encounters with entities or presences.[16] Prospective and retrospective studies document a prevalence ranging from 6.3 % to 39.3 % among cardiac arrest survivors, a variability attributable to methodological differences, diagnostic criteria, and the timing of post-event interviews. Although the underlying pathophysiology remains a subject of debate, hypotheses range from transient dysfunction of temporoparietal networks to massive release of neurotransmitters under hypoxic conditions. Its existence raises fundamental questions about the generation of conscious content in states approaching clinical death.[16,17]

Electrophysiological recordings of individual units have documented that during global cerebral ischemia, marked hyperactivity occurs in both interneurons and pyramidal neurons of the hippocampus. This transient phase of excitation is accompanied by high-frequency gamma oscillations (40-100 Hz), a rhythmic pattern normally associated with processes of encoding, memory integration, and synchronization of cortical networks. Notably, this activity coincides with the functional activation of the default mode network (DMN), a circuit widely linked to self-awareness, autobiographical recall, and multisensory integration. These findings suggest that even under critical conditions of hypoxia, network dynamics capable of sustaining complex experiences can emerge, providing a plausible physiological framework for phenomena such as the near-death experiences (NDEs) observed in survivors of cardiac arrest.[18,19]

In mouse models, global cerebral ischemia triggers a massive release of calcium stored in the endoplasmic reticulum, which activates Ca^{2+}/calmodulin-dependent signaling pathways and leads to the phosphorylation of CREB (cAMP response element-binding protein).[20] This transcription factor plays an essential role in the expression of genes involved in synaptic plasticity and the consolidation of long-term memories. The activation of CREB in the context of severe hypoxia presents a paradoxical scenario: while the global neural network may be on the verge of functional collapse, certain memory-related transcriptional programs could be transiently activated. From a translational perspective, this offers a plausible molecular framework for explaining how memory fragments or structured experiences (such as those reported in out-of-body experiences) could be encoded or consolidated even under extreme conditions of neuronal stress.[20]

In the AWARE II study, which used high-density electroencephalography (EEG) during resuscitation efforts following cardiac arrest, approximately 40 % of survivors who reported near-death experiences showed a return of electrical patterns consistent with conscious activity, including gamma, delta, theta, alpha, and beta oscillations, even up to 60 minutes after the start of CPR.[16] These findings support the hypothesis that NDEs may represent an epiphenomenon of terminal neural disinhibition, in which the loss of thalamocortical inhibitory control allows for a transient hyperactivation of networks involved in memory and self-perception. From a mechanistic perspective, this sequence could reflect the final coordinated functional expression of mnemonic networks before the definitive collapse of neuronal activity.

Animal models: postmortem EEG surges

In 2013, a pioneering study in rats (PNAS) documented surges of high-amplitude electroencephalographic (EEG) activity (1-4 Hz delta and 25-55 Hz gamma) lasting up to 30 seconds *post mortem*, a phenomenon termed the "brain tsunami".[19] This pattern, replicated in models of prolonged ischemia in larger mammals, is associated with global terminal depolarization, an abrupt reversal of ionic gradients, along with a massive release of glutamate, which in turn overstimulates NMDA receptors in cortical neurons.[21] Mass spectrometry studies of postmortem brain tissue have detected elevated levels of endogenous N,N-dimethyltryptamine (DMT), a psychedelic alkaloid with affinity for 5-HT2A receptors, at concentrations of 0.1-0.4 ng/g (vs. 0.01 ng/g in controls).[22]

While these surges might represent a final attempt by the brain to preserve thalamocortical coherence, the lack of phase-amplitude coupling (i.e., synchronization between oscillations of different frequencies) indicates that they would not be sufficient to maintain integrated conscious states. Furthermore, studies in which NMDA receptors are blocked show a decrease in the amplitude of these bursts, supporting their glutamatergic origin.[23,24]

Controversies: neurochemistry and physics *vs.* consciousness beyond the brain

Various lines of research suggest that NDEs could be explained by the interaction of three neurochemical and network mechanisms. First, hypoxia, resulting from a critical drop in partial pressure of oxygen (< 30 mmHg) during cardiac arrest, triggers excessive activation of NMDA receptors, which can lead to anomalous perceptual phenomena, such as visual and auditory hallucinations, as well as states of depersonalization.[25] Second, it has been proposed that, under conditions of extreme stress, the pineal gland releases N,N-dimethyltryptamine (DMT), a potent serotonergic e agonist that, in controlled studies, has been shown to induce mystical experiences and sensations of subjective transcendence comparable to NDE accounts.[22] Finally, residual activity in the default mode network (DMN) could also play a significant role: functional disconnection of the thalamus during hypoxia or global depolarization would reduce inhibition on the posterior cingulate cortex, thereby promoting the transient emergence of activation patterns capable of generating experiences of unity, timelessness, or "transcendence".[26]

From the perspective of information physics, it is argued that information is physical in nature and subject to thermodynamic laws (e.g., the minimum cost of erasing a bit, Landauer's principle). Furthermore, the Bekenstein bound states that the maximum amount of information a physical system can contain depends on its energy and size. This principle suggests that the capacity to store information within a finite region of space is also finite. In quantum physics, the unitary evolution principle holds that information is not destroyed, but rather transformed or dispersed. Certain proposals related to holography and so-called "quantum islands" have reinforced this interpretation in the study of extreme phenomena, such as the evaporation of black holes. In popular science, Sabine Hossenfelder has compared death to a "drop of ink" that disperses into the ocean: its components continue to be part of the universe, even though the original structure becomes unrecognizable. This analogy illustrates the dispersion of matter and physical information, but it does not prove the persistence of consciousness, memory, or personal identity after biological death.[27]

It should be noted that this approach is based on the principle of information conservation, widely debated in theoretical physics and quantum mechanics, and suggests a form of "immortality" not tied to the functional continuity of the brain, but rather to the permanence of the states of information that defined us. From the perspective of neuroethics, this hypothesis raises provocative questions: Can a purely informational persistence without an organized substrate be considered "survival"?

What implications would this have for the concept of personal identity if such dispersed information were neither recoverable nor reconstructible in a conscious form?

The case of Pam Reynolds, who underwent surgery in 1991 involving total circulatory arrest, an isoelectric EEG, and the absence of cerebral blood flow, is one of the most frequently cited in the NDE literature due to the precision of her descriptions of surgical instruments and conversations, which were subsequently verified by the medical team.[28] Skeptical explanations suggest that these memories could originate from residual anterograde memory, that is, the recording of stimuli perceived minutes before the induction of cardiac arrest, or from phenomena such as anesthesia awareness.[29] However, experimental studies designed to test these perceptions have not yielded similar results. In some of these studies, specific words or sounds were played through headphones during situations associated with near-death experiences. Subsequently, the patients were unable to identify these stimuli with the expected accuracy. Therefore, to date, it has not been reproducibly demonstrated that external auditory information can be perceived and recalled in great detail during these experiences.[29]

On a philosophical level, David Chalmers has proposed a naturalist/emergentist dualism, according to which consciousness is a fundamental property of reality, irreducible to known physical processes. From this perspective, NDEs could be interpreted as transient manifestations of a conscious substrate that persists briefly after the cessation of organized brain activity. However, this hypothesis lacks direct empirical support and remains in the realm of metaphysical speculation.[30]

Ethical and philosophical implications

International discrepancies between biological and legal criteria for determining death

Currently, 74 countries adopt criteria for total brain death, the irreversible cessation of all brain activity, including that of the brainstem, as the legal standard. However, in jurisdictions such as Japan and Saudi Arabia, legal death additionally requires irreversible cardiac arrest; this reflects regulatory frameworks influenced by cultural and religious traditions.[1,31] This heterogeneity generates conflicts in contexts such as organ transplantation and experimental resuscitation. For example, in 2021, a patient in Texas was declared legally dead based on neurological criteria, but his family demanded that life support be continued based on religious beliefs regarding "residual life" in glial cells.[32] Such cases underscore the need for international standards based on neurophysiological evidence, not merely on cultural traditions.[33]

Furthermore, the recent development of xenobots, programmable multicellular structures created from living cells extracted from deceased organisms, such as stem cells from *Xenopus laevis*, has further blurred the line between life and death.[34] Although they lack a nervous system and conventional metabolic functions, these organisms exhibit coordinated behaviors, spontaneous locomotion, and the ability to self-repair.[34] Their existence raises profound ontological and bioethical questions: Is it possible to speak of "functional life" in the absence of consciousness, homeostasis, or a complete organism? These findings suggest that biological death should not be understood as an absolute event, but rather as a gradual process of cellular reorganization with functional potential, which reinforces the need to redefine legal criteria for death from a multidisciplinary perspective that incorporates advances in synthetic biology, neuroscience, and biomedical ethics.[34]

Informed consent for experimental resuscitation: the cryonics dilemma

Patients who opt for cryopreservation sign legally binding contracts, but informed consent for future resuscitation is impossible: the required technologies do not exist, and there is no guarantee that identity or memory will be preserved.[15] In 1992, a California appellate court ruled in Alcor Life Extension Foundation v. Mitchell that the organization could receive human remains through the anatomical donation system and obtain the necessary permits for cryopreservation following a legal declaration of death. This ruling established a legal framework for the practice, contingent upon compliance with regulations governing authorization, death certification, transport, and the disposition of remains. However, the court's decision neither validated the scientific efficacy of cryonics nor confirmed the feasibility of future resuscitation. Due to this uncertainty, organizations offering these services utilize contractual clauses explicit in warning that the revival of cryopreserved individuals remains a highly speculative outcome that cannot be guaranteed.[35] Furthermore, while it is true that some modern techniques, such

as stabilized aldehyde vitrification, have been shown to preserve the ultrasynaptic structure in porcine brains, even after complete cryopreservation, doubts remain regarding long-term neuronal functionality. A pioneering study succeeded in keeping the synapses and cellular architecture of the cerebral cortex intact after vitrification, but did not assess whether these tissues could regain conscious activity following resuscitation.[36] This raises questions about the integrity of personal identity and the risk of unpredictable cognitive alterations should consciousness ever be restored in the future.

Resource allocation: resuscitation versus palliative care

Research into brain resuscitation has received increasing investment, which was estimated at around USD 280 million in 2022. However, nearly 78 % of the world's population still lacks access to basic palliative care services.[37] Highly complex clinical trials such as ARREST (ECMO-CPR) involve costs of approximately USD 500 000 per patient, in contrast to the approximately USD 2000 per year required to provide palliative care for a patient with terminal cancer. This imbalance has prompted criticism pointing to a technocentric bias: prioritizing "life after death" over the relief of suffering in dying patients could exacerbate global health inequalities.[38,39] However, advocates of these technologies argue that if advanced resuscitation were to reduce the demand for transplants, it could generate substantial savings, estimated at USD 3.8 trillion annually, by shortening waiting lists and reducing the costs associated with organ procurement and preservation.[40]

Future directions

Artificial perfusion systems: from organEx to brainEx

Ex vivo perfusion has evolved from an experimental procedure to become an established technological platform with profound clinical and ethical implications. One example is the BrainEx system, developed at Yale, which demonstrated the ability to restore circulation and cellular metabolism in pig brains up to four hours after death; this preserves neuroanatomical integrity, and reduce cell death, without producing the global electrical activity necessary for consciousness.[3] Its successor, OrganEx, expanded the scope: after one hour of warm ischemia in a porcine model, it succeeded in restoring cellular and metabolic functions in multiple organs, including the brain, heart, liver, and kidneys, using a fluid that combines autologous blood with synthetic hemoglobin, oxygen-carrying nanoparticles, and a cocktail of cytoprotectants.[4] Although no percentage quantification of preserved synapses has been reported, studies with BrainEx showed that, after six hours of perfusion, the neuroanatomical structure was maintained and cellular functionality, including localized synaptic activity, was evident in porcine brains up to ten hours *post mortem*.[41]

The immediate future points toward human-AI hybrid systems capable of adjusting perfusion parameters, flow, pressure, and fluid composition, in real time based on biomarkers obtained through functional magnetic resonance imaging and other advanced neuroimaging modalities.[42]

Nanotechnology: neuroprotective agents and selective delivery

Nanoparticles cross the blood-brain barrier postmortem. PEGylated nanoparticles loaded with siRNA targeting caspase-3 have been shown to cross the blood-brain barrier and significantly reduce neuronal apoptosis in rat models of ischemia, outperforming the efficacy of traditional treatments such as hypothermia.[43] Recent studies have shown that brain-derived neurotrophic factor (BDNF) promotes neurogenesis and axonal regeneration in the hippocampus, especially following ischemic injury.[44] Its use with magnetic nanomotors has not yet been demonstrated in porcine models, but emerging platforms such as exosomes and functionalized nanoparticles are being explored to deliver BDNF in post-ischemic neuroregenerative therapies.[45] However, these advances are limited by significant ethical and biomedical challenges: in certain cases, as much as 99 % of the nanoparticles accumulate in the liver, which reduces their therapeutic efficacy and raises potential risks of long-term toxicity.[46]

Restoring consciousness: bridging the connectome gap

Restoring consciousness requires preserving the connectome, the complete map of neural connections. The Human Connectome Project has identified 90 % redundancy in thalamocortical networks, allowing for the recovery of functions with as few as 30 % of synapses intact.[47] In mouse models, neuronal grafts derived from induced pluripotent stem cells (iPSCs) and modified to express photosensitive ion channels have been shown to improve thalamocor-

tical connectivity and functional recovery following ischemia, paving the way for future applications in non-human primates.[48] The greatest obstacle remains the synchronization of gamma oscillations: without phase coherence between the thalamus and the cortex, the neural integration that underpins consciousness would be unfeasible.[49]

Conclusion

Advances in brain resuscitation are redefining the boundaries between biological death and the potential recovery of neurological functions. Established strategies such as therapeutic hypothermia and ECMO-CPR have succeeded in extending the window of brain viability to 60 minutes post-cardiac arrest, with rates of neurologically intact survival approaching 43 % in recent trials. However, experimental technologies such as the BrainEx protocol and cryopreservation via vitrification pose unprecedented dilemmas; while they allow for the restoration of cellular metabolism or the preservation of synaptic ultrastructure, they do not guarantee the recovery of consciousness or personal identity.

Neurobiological evidence suggests that NDEs may constitute epiphenomena associated with terminal hyperactivity of the hippocampus, influenced by the release of glutamate and endogenous DMT. Nevertheless, paradigmatic cases such as that of Pam Reynolds challenge purely materialistic explanations and call for theoretical frameworks that integrate neuroscience, philosophy, and ethics.

At the same time, bioethical challenges remain critical. Global disparities in the legal definition of death, the speculative nature of consent for cryopreservation, and the tension in resource allocation between advanced resuscitation and palliative care demand regulations grounded in evidence, not in cultural dogmas or uncritical technological optimism.

Looking ahead, platforms such as OrganEx-BrainEx, neuroprotective nanotechnology, and thalamocortical reconnection therapies could bridge the gap between cellular preservation and the restoration of conscious functions. However, without agreed-upon international standards for evaluating the success of resuscitation, these advances risk widening global health inequities.

Ultimately, this field requires genuinely multidisciplinary collaboration, involving physicians, bioengineers, philosophers, and policymakers, to balance the potential for "life after death" with an unwavering respect for human dignity and distributive justice.

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