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Review

Heart Transplantation Post-donation After Circulatory Death: Current Status and Future Potential

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Abstract

Heart transplantation enhances the quality of life and survival rate of patients with end-stage heart failure. However, the biggest obstacle remains the insufficient supply of cardiac grafts, which has caused the global waitlist for heart transplants to increase. Subsequently, donation after circulatory death (DCD) has emerged as a potential solution to alleviate the insufficient supply of cardiac grafts, potentially offering new opportunities for terminally ill patients. Over the past five years, the number of DCD heart transplants has increased, with increasing success rates reported by organ transplantation centers in Britain, Australia, and the United States. This trend highlights the growing recognition of the potential for DCD-related heart transplantations. Unlike traditional donation after brain death (DBD), DCD requires an ischemic period before implantation in the recipient. Presently, no perfect solution exists to avoid or alleviate ischemic injury to the donor myocardium, which may affect the quality and viability of the DCD grafts. Therefore, the future use of DCD donor hearts hinges on scientific advancements addressing challenges such as optimizing donor heart preservation and transportation. Meanwhile, collaboration among surgical teams and public understanding and support are also crucial. This review summarizes the phylogeny and status of DCD heart transplantation and analyzes specific aspects, including transplantation protocols, clinical cases, and challenges. The objective was to anticipate further roles for DCD heart transplantation that can improve survival and quality of life for patients with end-stage heart disease.

Keywords

donation after circulatory death; donation after brain death; heart transplantation; ischemia-reperfusion injury; machine perfusion; complication

Introduction

Cardiovascular diseases represent increasingly significant health challenges worldwide; heart failure cases, a major manifestation of cardiovascular disease, have risen dramatically in recent years [1]. Indeed, the number of heart failure patients doubled in China from approximately 4.5 million in 2018 to 8.9 million by 2021 [2]. Moreover, the number of patients with heart failure in the United States is estimated to reach 8.5 million by 2030; the number of patients has increased by 2.5 million in 15 years, a relative increase of 42% [3]. This upward trend is expected to continue due to aging populations and the increasing prevalence of risk factors such as diabetes and hypertension. Heart transplantation has emerged as the most effective treatment for end-stage heart disease, with recipients now surviving more than 15 years post-transplantation, thus offering hope to patients who have exhausted conventional medical therapies [4].

Meanwhile, the demand for heart transplants far exceeds the available supply, necessitating innovative approaches to expand the donor pool. Thus, donation after circulatory death (DCD) has become an important solution in the heart transplant donor pool, addressing the current critical shortage in donor hearts [5]. DCD, once considered unsuitable for heart transplantation, has gained acceptance due to advances in preservation techniques and recipient management. This approach has significantly increased the number of viable donor hearts, providing a valuable resource for patients awaiting transplantation [6]. Furthermore, improvements in immunosuppressive therapies have reduced the risk of organ rejection, although managing long-term complications remains a significant challenge [7].

This review aims to provide a comprehensive overview of the current status of heart transplantation, discuss the importance of DCD in expanding the donor pool, and examine recent advances in transplantation technology and postoperative care. Moreover, by summarizing the latest research and clinical practices, this review seeks to contribute to the continuing efforts to improve outcomes for heart transplant recipients and address the growing global burden of end-stage heart disease.

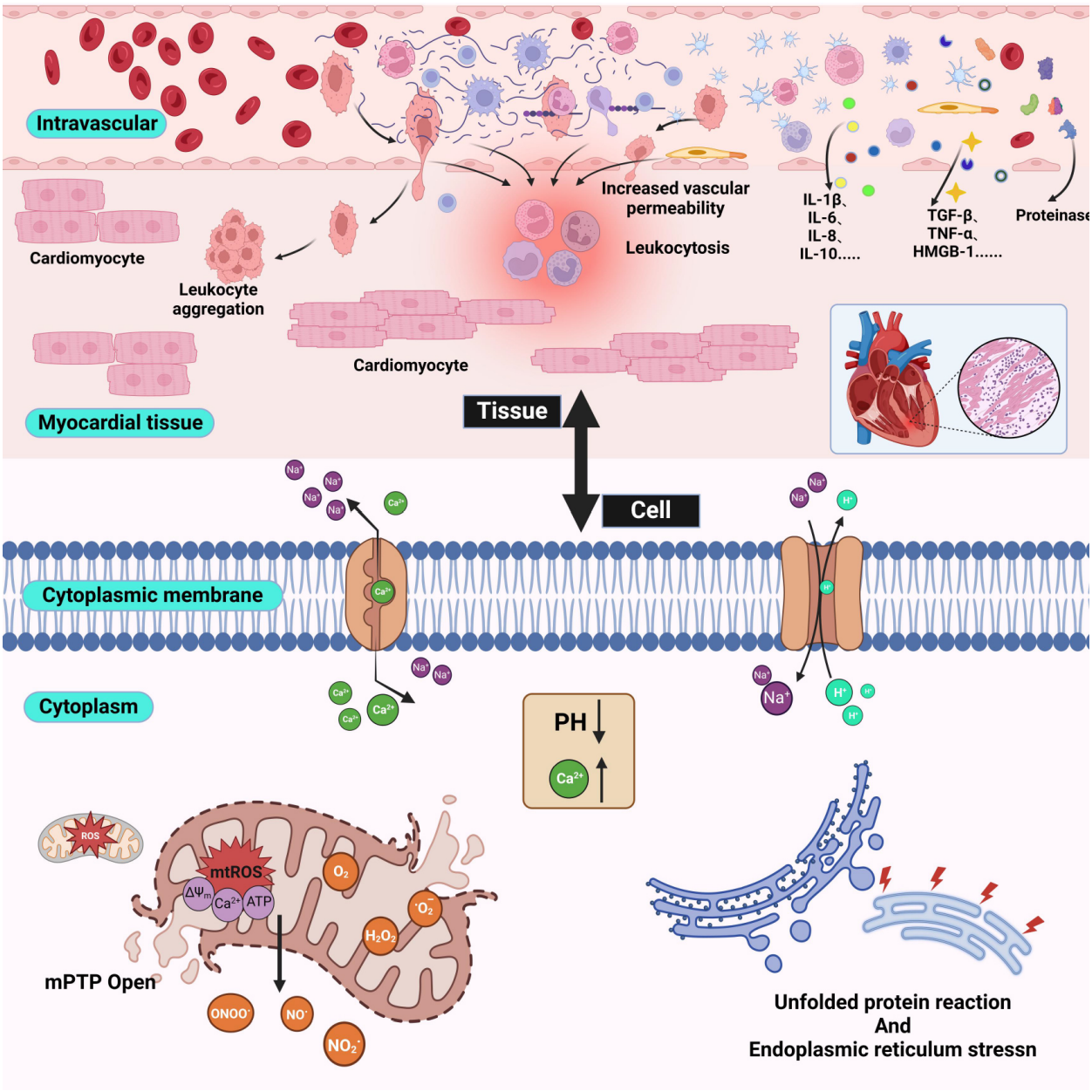

Fig. 1. Pathophysiological mechanism of ischemia-reperfusion injury. IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; HMGB-1, high mobility group box 1; PH, potential of hydrogen; mPTP, mitochondrial permeability transition pore. This figure was created using BioRender.com.

DCD Heart Transplantation

Heart transplantation remains the gold standard for treating end-stage heart failure; however, the persistent shortage of donor hearts has driven the exploration of alternative donor sources. Among these, DCD has emerged as a critical strategy to expand the donor pool. This section provides an overview of DCD heart transplantation, focusing on the unique pathophysiology of this technique compared with DBD and the latest clinical advancements.

Unique Pathophysiology of DCD

After a period of cardiac ischemia, the myocardial ischemia-reperfusion injury (IRI) that occurs when the blood supply is suddenly restored affects the prognosis of patients [8–10]. During the ischemic period, cardiomyocytes lack sufficient oxygen and nutritional supply, and their metabolism is disordered, leading to chain reactions inside and outside the cells. Reperfusion therapy for the rapid recovery of the myocardial blood supply is the most effective treatment to reduce ischemic injury and limit the

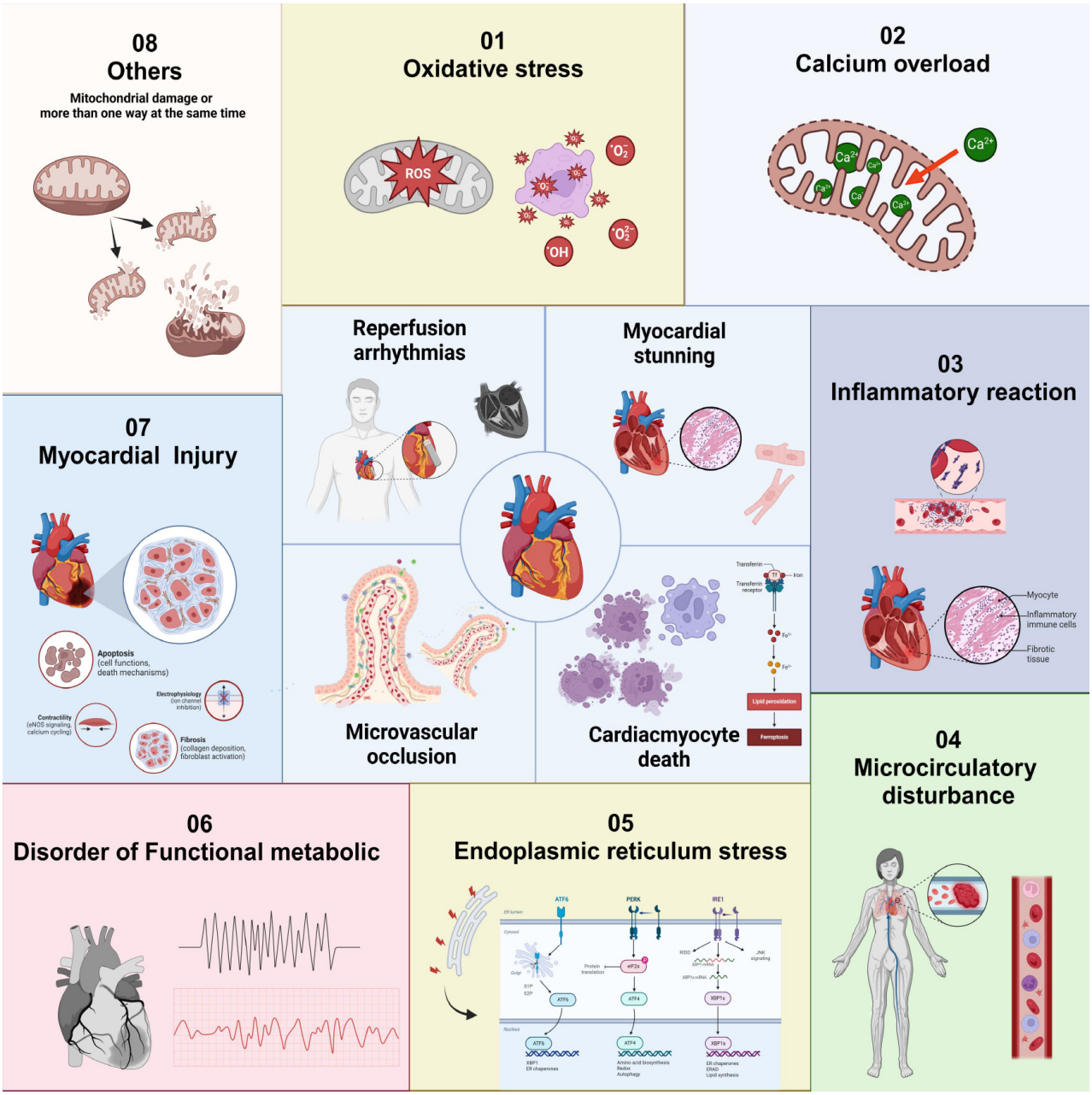

Fig. 2. Myocardial ischemia-reperfusion injury. There are four main manifestations of IRI: reperfusion arrhythmia, myocardial stunning, microvascular obstruction and fatal cardiacmyocyte death, which involve complex pathophysiological processes. At present, the relatively certain mechanisms are: oxidative stress, calcium overload, inflammatory reaction, microcirculation disturbance, endoplasmic reticulum stress, disorder of functional metabolic, myocardial cell damage and others. ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ATF6, activating transcription factor 6; PERK, pKR-like endoplasmic reticulum kinase; IRE1, inositol requiring enzyme 1; eIF2α, eukaryotic initiation factor 2 alpha; ATF4, activating transcription factor 4; XBP1, X-box binding protein 1; RIDD, regulated IRE1-dependent decay; JNK, c-Jun N-terminal kinase; ERAD, ER-associated degradation. This figure was created using BioRender.com.

size of the infarct [11]. However, the additional myocardial injury caused by ischemia/reperfusion accounts for half of the final myocardial injury. There are four main ischemia/reperfusion injury manifestations: reperfusion arrhythmia, myocardial stunning, microvascular obstruction, and fatal myocardial cell death [11,12]. These processes involve complex pathophysiological developments (Fig. 1). The major mechanisms involved are oxidative stress, calcium overload, inflammatory reaction, microcirculation disturbance, endoplasmic reticulum stress (ERS), functional metabolism disorders, and myocardial cell damage (Fig. 2) [13,14].

During the ischemic phase, cardiomyocytes suffer from oxygen and nutrient deprivation, leading to adenosine triphosphate (ATP) depletion and the accumulation of metabolic byproducts, such as lactate and hydrogen ions. This metabolic dysfunction disrupts ion homeostasis, particularly calcium regulation, resulting in intracellular calcium overload upon reperfusion [15,16]. Moreover, the sudden restoration of blood flow during reperfusion generates a burst of reactive oxygen species (ROS), exacerbating cellular damage through lipid peroxidation, protein denaturation, and DNA fragmentation [17]. Oxidative stress further activates inflammatory pathways, releasing proinflammatory cytokines (interleukin-1β, interleukin-6, tumor necrosis factor α) and the recruitment of leukocytes, which contribute to endothelial dysfunction and microvascular obstruction. This "no-reflow" phenomenon impairs tissue perfusion and exacerbates ischemic injury. Additionally, ERS is activated during reperfusion, disrupting protein folding and calcium homeostasis, and triggering the unfolded protein response, which can lead to apoptosis [18]. Mitochondrial dysfunction, a hallmark of IRI, further exacerbates injury by impairing ATP production and increasing the generation of ROS, creating a vicious cycle of cellular damage [19,20]. These mechanisms are the primary drivers of the ongoing debate surrounding the use of DCD hearts, as these mechanisms contribute to concerns regarding graft dysfunction and post-transplant complications. However, significant advancements have been made in addressing these challenges. Normothermic regional perfusion (NRP) and *ex situ* machine perfusion (MP) systems, such as the Organ Care System (OCS) Heart System, have emerged as effective strategies to minimize warm ischemic injury and preserve myocardial viability [21]. Additionally, preclinical studies have shown promise in pharmacological interventions targeting key pathways involved in IRI, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), Notch, Wingless/Integrated/β-catenin (Wnt/β-catenin), and nuclear factor erythroid 2–related factor 2/heme oxygenase-1 (Nrf2/HO-1) [22–25]. For example, in DCD models, oxidative stress and inflammation inhibitors have demonstrated cardioprotective effects [26,27]. Meanwhile, ischemic preconditioning and postconditioning techniques, which involve brief cycles of ischemia and reperfusion before or after the main ischemic event, have also shown potential to activate endogenous protective mechanisms.

Nonetheless, despite these advancements, the heterogeneity of DCD donors and the complexity of the IRI pathways necessitate further research to optimize preservation techniques, develop targeted therapies, and establish standardized protocols through multicenter trials.

Comparison between DBD and DCD Heart Transplantation

Heart transplantation relies on two primary donor sources: DBD and DCD (Table 1). In DBD, organs are retrieved from donors who have suffered catastrophic brain injuries, leading to irreversible loss of brain function, but whose hearts continue to beat with ventilator support, which allows for a controlled and thorough evaluation of cardiac function before organ procurement, including coronary circulation. Further, DBD has traditionally been the dominant source of donor hearts worldwide. Comparatively, unlike DBD, DCD donors are those who have suffered catastrophic brain injuries but do not meet the criteria for brain death [28]. Subsequently, following the withdrawal of life support, circulatory arrest occurs, after which a mandatory "stand-off" period (typically 5 minutes) is performed to confirm death before organ recovery [29]. The ischemic time involved in DCD heart transplantation is more complicated than that of DBD. The hearts transplanted following DCD will experience warm ischemic time (WIT) without blood supply before procurement. WIT is typically defined as the interval between the withdrawal of life-sustaining therapy (WLST) and the initiation of cold perfusion or cardioplegic arrest [30,31]. A more specific subset, referred to as functional warm ischemic time (FWIT), is defined as the duration from the onset of significant hypoperfusion, typically when mean arterial pressure $<$50 mmHg or SpO_2 $<$70%, to the initiation of organ preservation (either cold perfusion or NRP-induced reperfusion) [32,33]. Meanwhile, prolonging the FWIT beyond 30 minutes has been associated with a significantly increased risk of primary graft dysfunction and adverse post-transplant outcomes [34,35]. As the WIT increases, cells continue to metabolize without an adequate oxygen supply, leading to increased cell death, which directly determines the feasibility of heart transplantation and the prognosis of recipients.

The evolution of DCD protocols, particularly the transition from the original Maastricht Classification (1995) to the modified Maastricht Classification (Paris 2013), has further refined donor selection criteria and expanded the donor pool [36,37]. In the largest single-center analysis comparing DCD and DBD heart transplantation outcomes, Siddiqi *et al*. [38] reported no significant differences in one-year recipient survival, incidence of severe primary graft dysfunction (PGD), treated rejection, or cardiac allograft vasculopathy [36,39]. A multicenter retrospective cohort study in the United Kingdom demonstrated that the use of DCD donors was associated with a 28% overall increase in heart transplant procedures compared to DBD donors; meanwhile, early post-transplant survival at 30 and 90 days, as well as hospital length of stay, remained comparable between the two groups [40]. Similarly, a meta-analysis of DCD heart transplantation programs in the United States, the United Kingdom, and Australia demonstrated that early and intermediate post-transplant outcomes were compara-

Table 1. Comparison between the two heart transplantation schemes—DBD and DCD.

Category			Countries	Advantages	Disadvantages
DBD			Germany, Latvia, Bulgaria, Croatia, Cyprus, Poland, Denmark, Malta, Estonia, India, Romania, Cuba, Slovakia, Peru, Romania, Hungary, Belarus, Kuwait, Slovenia, All-DCD countries.	① Detailed assessment and optimization of heart function before retrieval. ② Short period of warm ischemia. ③ Well-established treatment with excellent long-term outcomes.	① The heart is subjected to a catecholamine surge during brain death. ② Limited pool of potential donors.
DCD	uDCD	Category I: found dead. Category II: witnessed cardiac arrest. Category IV: cardiac arrest while alive but brain dead.	Portugal, Spain, Israel, Japan.	① Extended pool of potential donors. ② Heart not subjected to catecholamine surge before retrieval. ③ Good short-term outcomes (in limited experience to date).	① Limited the time window, and a potential donor may not meet the circulatory death criteria after withdrawal of support. ② Longer period of warm ischemia; cold ischemia time is shorter when perfused *in vitro*. ③ Reduced cardiac function due to longer ischemia time makes its functional assessment more challenging, especially when *in vivo* NRP or *ex vivo* perfusion techniques are not used. ④ Long-term outcome after transplantation is uncertain. ⑤ Ethical and moral issues. ⑥ High cost of the machine perfusion device.
	cDCD	Category III: withdrawal of life-sustaining therapy. (Planned withdrawal of life-sustaining therapy; expected CA)	Australia, China, Austria, Belgium, Canada, Czech Republic, France, Ireland, Italy, Sweden, Spain, Netherlands, New Zealand, Norway, Argentina, Lithuania, and the UK. Switzerland, Finland, Britain, and the US.		

DBD, donation after brain death; DCD, donation after circulatory death; uDCD, uncontrolled donation after circulatory death; cDCD, controlled donation after circulatory death; NPR, normothermic regional perfusion.

ble between DCD and DBD donors [41]. Recent single-center and multi-center long-term follow-up data revealed no significant difference in five-year survival rates between DCD and DBD heart transplant recipients, further supporting the viability of DCD heart transplantation as a comparable alternative [6,42]. In response to the persistent organ shortage, the concept of marginal donor hearts—those with high-risk factors or a degree of mismatch with recipients—has increased. While some studies have shown promising results with marginal donors, most evidence is provided by single-center retrospective studies, highlighting the need for larger, multicenter trials to establish standardized protocols. Thus, caution is warranted in the clinical use of marginal donors, as their long-term outcomes remain uncertain.

In conclusion, while DBD remains the gold standard for heart transplantation, DCD is emerging as a critical alternative to address the global donor shortage. As the field evolves, further research and innovation are essential to optimize DCD protocols, expand the donor pool, and improve outcomes for patients with end-stage heart failure.

Clinical Status of DCD Heart Transplantation

Notably, Christiaan Barnard performed the first human DCD heart transplant in 1967 [43]. However, the outcomes were suboptimal, highlighting the challenges of early transplantation efforts. Similarly, the first pediatric heart transplant was conducted in December 1967 in New York using an anencephalic donor without cardiopulmonary bypass; however, the recipient unfortunately died six hours

post-transplant [44]. These early attempts underscore the technical and physiological hurdles of heart transplantation procedures. Nonetheless, the landscape of heart transplantation changed significantly in 1980 following the establishment of brain death criteria. Over the subsequent 36 years, most heart donations were obtained from DBD donors; however, the persistent shortage of DBD donors prompted the re-emergence of DCD heart transplantation in July 2014 [45]. The Sydney group pioneered this revival by developing the direct procurement protocol (DPP) and successfully completed three adult DCD heart transplants. Furthermore, their subsequent DCD heart transplant procedures achieved a remarkable success rate of 96%, demonstrating the feasibility and potential of DCD hearts in clinical practice [46]. Thus, the history of heart transplantation has been marked by significant milestones, and DCD has emerged as a pivotal development in addressing the global shortage of donor hearts.

Building on the success of the Sydney group, the Papworth group in the United Kingdom introduced NRP, followed by static cold storage (SCS), and reported successful transplant cases using this approach [47]. Further advancements were made by Tchana-Sato *et al*. [48], who integrated SCS and NRP to refine organ retrieval techniques, leading to the first successful DCD heart transplant performed in Belgium. The Royal Papworth Hospital in Cambridge performed the first adult DCD heart transplant in Europe in 2015, marking a significant milestone in a region that previously relied exclusively on DBD donors. Subsequently, the number of adult DCD heart transplants has steadily increased, reflecting the maturation of DCD transplantation technology and its growing acceptance worldwide. A groundbreaking achievement in pediatric DCD heart transplantation occurred at Great Ormond Street Children's Hospital in London, in collaboration with the Royal Papworth Hospital and the National Health Service Blood and Transplantation Center. Using the OCS, these institutions successfully performed the world's first pediatric DCD heart transplant. This breakthrough demonstrated the feasibility of DCD hearts in pediatric transplantation, offering hope to critically ill children who face the highest mortality rates on transplantation waiting lists.

Integrating DCD hearts into the donor pool can potentially increase the annual number of heart transplants by 600 to 1200 cases. Thus, countries such as Australia, Belgium, the Netherlands, Spain, the United Kingdom, and the United States have gradually increased the proportion of DCD donors in organ donation programs [49–52]. Moreover, the inclusion of DCD hearts could increase heart transplant activity by 17% to 30%, providing a lifeline for patients who would otherwise face a poor prognosis [40,53]. As of 2023, the use of hearts from DCD donors has steadily increased, and DCD donor heart transplantations are currently being performed in over 300 transplant centers. However, despite these advancements, the current demand for heart transplants still far exceeds the available supply, highlighting the urgent need for continued innovation and the expansion of donor sources.

Protection Strategy for the Donor Heart

Organ Preservation Technology

SCS (performed at 4 °C) represents the current standard preservation technique for transplanted hearts. This method is simple and economical, but results in cold ischemic injury, which increases with preservation time; thus, SCS is usually limited to 4–6 hours. Comparatively, the Paragonix SherpaPak™ Cardiac Transport System (PSP), an improved form of SCS, maintains a constant, uniform, and controlled temperature between 4 °C and 8 °C to minimize tissue injury caused by exposure to ice-cold temperatures [18]. In the GUARDIAN study—an observational study analyzing adult and pediatric patients whose donor hearts were preserved and transported using either PSP or conventional cold storage methods—data from 877 patients enrolled in the Guardian heart registry by 16 US centers were analyzed. A propensity-matched analysis of two cohorts comprising 249 patients based on the technique of graft preservation showed no statistically significant difference in 1-year survival (p = 0.12). However, the incidence of severe PGD was significantly lower following PSP preservation compared to cold storage (4% vs. 10%; p = 0.01) [54]. Furthermore, in a recent matched cohort analysis of 87 patients in each group (PSP vs. SCS), PSP significantly reduced the post-transplant costs, underscoring the clinical and economic benefits of reduced severe PGD incidence [55]. MP organ preservation techniques include normothermic machine perfusion (NMP), sub-normothermic machine perfusion (SNMP), hypothermic oxygenated machine perfusion (HOPE), and hypothermic machine perfusion (HMP), as well as new preservation technologies such as ultra-low temperature preservation (Table 2, Ref. [46,56]) [57,58]. Compared with SCS, the *in vitro* perfusion systems continuously deliver nutrients through the inherent pipeline to achieve both simultaneous preservation and repair. Moreover, *in vitro* perfusion systems eliminate the metabolic wastes, provide the basic substances of organ metabolism during organ preservation under different temperature conditions, and reduce the damage of cold ischemia to myocardial and epithelial cells. Thus, these systems not only prolong organ preservation time but also evaluate the function of isolated organs and improve organ quality, thereby providing more time for donor heart transfer and transplantation, decreasing the incidence of postoperative complications, and improving marginal organs. MP applied to DCD heart transplantation is divided into NMP and HMP, which are more in line with the physiological state than SCS; however, the cost for this technique is high

Table 2. Preservation technologies for the donor hearts.

Preservation technology		Temperature	Applied	Evaluation
SCS		4 °C	Yes	(1) The standard organ transplantation preservation technique. (2) Leads to organ cold ischemia injury, and is impossible to evaluate organ function effectively during cold preservation. (3) This method is simple and inexpensive, but produces cold ischemic injury, which is positively related to the preservation time; the preservation time only lasts 4–6 hours.
MP	NMP	~32–37 °C	Yes	(1) Reversal of the warm ischemia injury can minimize the ischemic injury of the DCD heart, which is beneficial to the recovery and preservation of donor hearts in the process of remote organ acquisition, and can assess the viability of the donor heart before implantation [46]. (2) It is a preservation method close to physiological state, which can make the donor heart remain available for ≥12 hours *in vitro* [56]. (3) Limited by the high cost of normal temperature machine perfusion and the lack of suitable machines for transporting DCD hearts of infants. (4) Vascular intubation before death and circulatory reconstruction after death touch on ethical issues.
	SNMP	~20–32 °C	No	/
	HOPE	~0–12 °C	No	/
	HMP	~0–12 °C	Yes	(1) Provide a perfusion solution rich in oxygenated nutrition while maintaining a low degree of myocardial metabolism. (2) The limitation is that it is impossible to evaluate the metabolism or function of the stagnant and non-beating heart, which prevents the clinical transformation of this technology in the DCD environment.
	Ultra-low temperature preservation	~ –6 to –4 °C	No	/
	Others	/	/	The Steen Heart Preservation System, developed by a Swedish team, and the HeartPort System and LifeCradle Heart Perfusion System, developed by an American team, are still in the research stage.

SCS, static cold storage; DCD, donation after circulatory death; MP, machine perfusion; NMP, normothermic machine perfusion; SNMP, subnormothermic machine perfusion; HOPE, hypothermic oxygenated perfusion; HMP, hypothermic machine perfusion.

and can only be applied for a limited period. NMP minimizes the ischemic injury of DCD hearts and is beneficial to the recovery and preservation of donor hearts in the process of remote organ acquisition; NMP is a more physiological preservation method that keeps the donor heart *in vitro* for over 12 hours [56,59]. However, NMP is limited by the high cost of machine perfusion at room temperature and the lack of a suitable machine for transporting the heart of an infant DCD. The vascular intubation before death and the circulatory reconstruction after death also raise ethical issues. Further, HMP, which provides perfusion fluid rich in oxygenated nutrition while maintaining a low degree of myocardial metabolism, is limited in that it is impossible to evaluate the metabolism or function of the stagnant and non-beating heart, which prevents the clinical transformation of this technology in DCD cases. Further research should promote the continuous optimization of perfusion solution formulas, the constant improvement in evaluation schemes, and the emergence of new treatment methods. Thus, MP technology is expected to become the standard method of DCD and marginal donor hearts, and an effective extension of the static cold preservation method of the heart. Although MP has improved donor heart preservation, ischemic injury still inevitably occurs, which affects

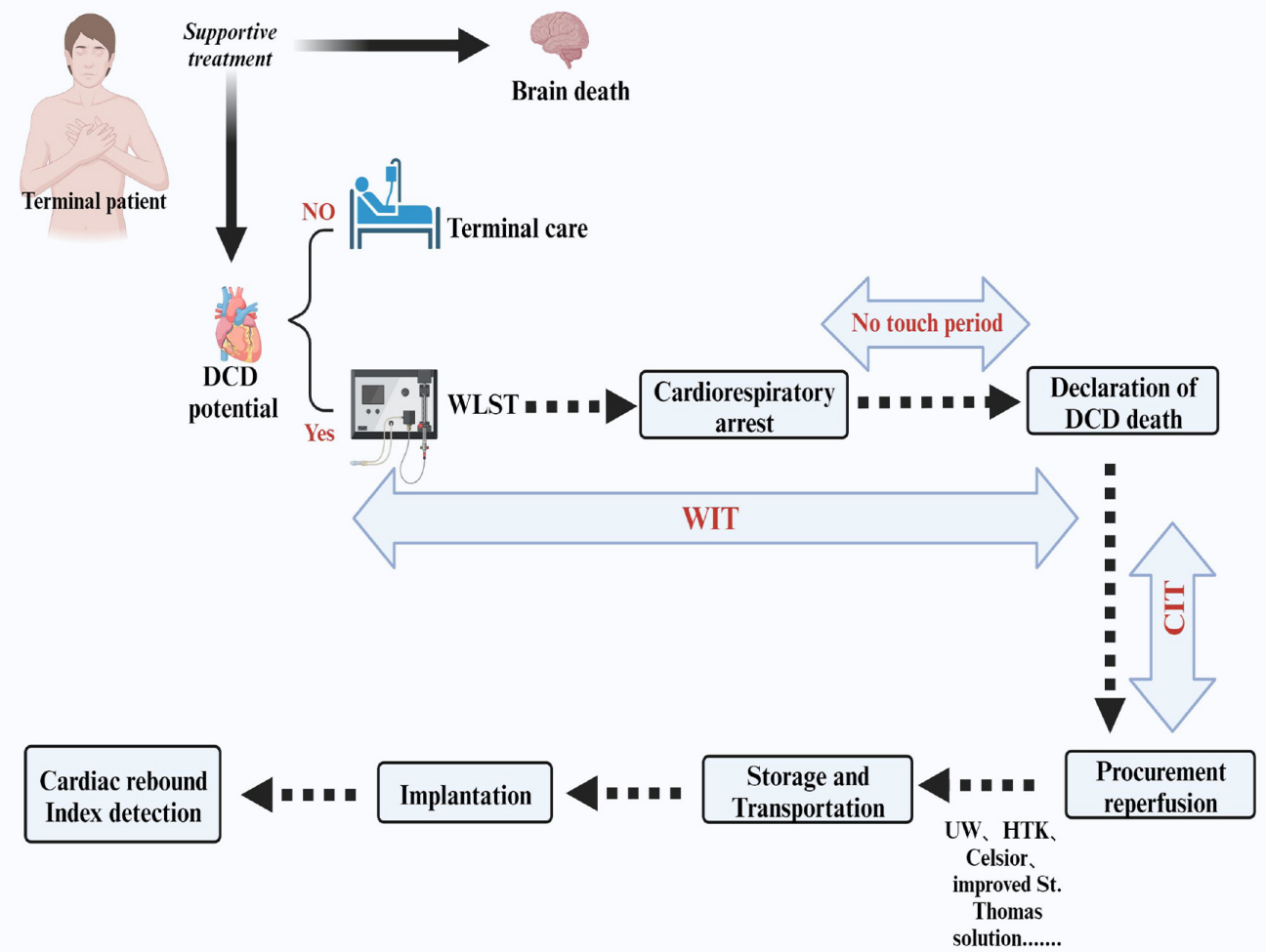

Fig. 3. Heart donation program after circulatory death. DCD, donation after circulatory death; WLST, withdrawal of life-sustaining therapy;WIT, warm ischemic time; CIT, cold ischemic time; UW, university of wisconsin; HTK, histidine tryptophan ketoglutarate. This figure was created using BioRender.com.

the prognosis of patients. To solve the problem of ischemic injury in the heart transplantation process, the First Affiliated Hospital of Sun Yat-sen University team developed and performed the first ischemia-free heart transplantation using the perfusion system independently developed in June 2021 [60]—this promoted a favorable prognosis for the patient. Theoretically, this technology avoids the ischemic injury to the heart and provides new possibilities for improving the quality of the donor heart; however, its clinical efficacy needs to be validated in further clinical research [61].

Resuscitation and evaluation of the DCD heart rely primarily on two technical strategies: thoraco–abdominal normothermic regional perfusion (TA-NRP) or direct procurement using machine perfusion (DP-MP). TA-NRP supports *in situ* warm perfusion via extracorporeal membrane oxygenation (ECMO) before retrieval. Meanwhile, DP-MP refers to a method of heart retrieval where the donor heart is immediately procured after circulatory death is confirmed and then placed directly on a machine perfusion system to resuscitate and preserve it. The OCS™ Heart System is the primary platform for maintaining and evaluating donor heart viability in DCD heart transplantations that utilize DP-MP. As the most widely used portable warm perfusion and monitoring device for DCD hearts, although OCS preservation allows for longer storage durations than traditional SCS, the OCS in DCD has demonstrated short-term clinical outcomes comparable to those of DBD hearts preserved via SCS [46,62,63]. According to a recent study, a 100% survival rate was observed at 3 months for recipients of DCD hearts and marginal donor hearts preserved using the OCS [36]. Furthermore, using OCS has been associated with reduced severe post-transplant complications, with patient survival rates reaching 94% and no significant PGD observed within the first 24 hours post-transplantation [64,65]. Indeed, Messer *et al.* [62] also compared outcomes between DPP combined with OCS and TA-NRP combined with OCS in DCD heart transplantation, and found no significant differences in 30-day and 90-day survival rates. The Steen Heart Preservation System is another dynamic perfusion

Table 3. Different cardioprotective solutions.

Types		Composition	Characteristics	Advantages	Disadvantages
Intracellular	UW	High-energy phosphate precursors (adenosine and phosphate), osmotic agents (lactobionic acid and raffinose), and antioxidants (allopurinol and glutathione)	High potassium, high viscosity, and high osmotic pressure.	① Alleviates cell edema and oxidative damage mediated by free radicals. ② Rapidly stops the heart in a high K^+ environment.	① Releases large amounts of high potassium solution during donor heart reperfusion, resulting in bradycardia and hypertension. ② Highly viscous, which is not conducive to rapid and sufficient heart perfusion.
Extracellular	HTK	Histidine, histidine buffer system, tryptophan, oxygen radical scavenger (mannitol), and substrates of high-energy compounds (α-ketodiacid and tryptophan)	Low K^+ content, powerful buffering capacity, low viscosity, and lower price than UW solution [80].	Low viscosity enables a rapid spread to the interstitial space, reducing the pre-flushing time.	Relatively low K^+ content that cannot induce rapid cardiac arrest.
	Celsior	Histidine/lactouronic acid buffer system and hydroxyl radical scavengers, such as reduced glutathione, histidine, and mannitol	Low potassium, high sodium, high magnesium, and low pH.	① Reduces cell edema and cell damage. ② Prevents acidosis. ③ Low incidence of postoperative vascular disease and chronic rejection [81].	Long-term preservation leads to myocardial edema.
	Del Nido	Plasma-lyte A, mannitol, magnesium sulfate, sodium bicarbonate, potassium chloride, lidocaine, and 20% blood.	Low potassium and an increased crystalline composition.	① Extended ischemic tolerance of a single infusion, which reduces repeated perfusion. ② Induces arrest and a strong myocardial protection.	The effects of long-term preservation are unclear; mainly designed for short-term cardiac arrest.

UW, university of wisconsin; HTK, histidine tryptophan ketoglutarate.

system that maintains donor heart function through continuous perfusion. This system has shown promising results in clinical trials, particularly in extending preservation time. Further, recent studies indicate that hearts preserved with the Steen system exhibit a low incidence of PGD post-transplantation [66]. Currently, a Swedish team is conducting a multi-center clinical trial to investigate the long-term effectiveness of the system further [67]. Early laboratory results suggest that the Heart-Port system can successfully prolong preservation while maintaining good heart function [68]; preliminary clinical trials are underway to assess its clinical application. The Life-Cradle system, another innovative perfusion preservation technology, aims to provide a more physiological environment to improve donor heart survival rates. Research by an American team has shown that hearts preserved using the Life-Cradle system exhibit better post-transplant function and reduced complications [69]; the system is undergoing clinical trials to determine its effectiveness across various heart transplants. Similarly, the XVIVO Hypothermic Oxygenated Perfusion (HOPE) System, developed by XVIVO Perfusion AB (Sweden), adopts a physiological preservation approach and preserves the heart in a temperature-controlled reservoir at 8 °C; meanwhile, a pressure-regulated roller pump maintains an aortic root pressure of 20 mmHg with a flow rate of 100–200 cc/min, mimicking the natural environment of the heart during preservation through temperature control and perfusion. This setup enables safe and efficient long-distance transport and offers protection against ischemia-related dysfunction, particularly in marginal donor hearts. Notably, the NIHP2019 study, a multinational, multicenter, randomized, controlled trial, demonstrated a 44% risk reduction in the composite primary endpoint of cardiac-related deaths, moderate or severe PGD, acute cellular rejection $\geq$2R, or graft failure within 30 days for XVIVO vs. SCS preservation [70,71]. Nevertheless, the XVIVO sys-

tem is currently in clinical trials to determine its effectiveness across various heart transplants [71–76].

In conclusion, these advanced preservation systems, OCS, Steen, Heart-Port, Life-Cradle, and XVIVO, represent significant advancements in DCD heart transplantation, offering promising solutions to extend the preservation time, reduce ischemic injury, and improve post-transplant outcomes. Continued research and clinical trials are essential to establish the long-term benefits and broaden the adoption of these technologies in clinical practice. However, great differences exist in the cost of the above heart preservation and transportation methods: Comparisons of the two methods of procuring hearts from DCD donors indicated the direct cost of TA-NRP was USD 155,955 compared to USD 223,399 for DP-NMP ($p = 0.21$) [77]. The OCS cost included the console costs of about USD 275,000, and the single-use components cost of USD 38,000–55,000 [78]. In addition, the OCS requires a maintenance service for over 10 years. Hence, as a traditional organ preservation method, SCS is much cheaper, costing about USD 55–162 [79]. However, studies demonstrate that 100% of hearts from NRP donors are used following assessment and acceptance for transplantation [78].

Heart Preservation

The heart donation process involves a critical ischemic period following circulatory arrest, necessitating perfusion to mitigate myocardial cell damage during donor heart acquisition (Fig. 3). Currently, the university of wisconsin solution (UW), histidine tryptophan ketoglutarate solution (HTK), and Celsior solutions are the most commonly used perfusion fluids for myocardial protection in adults during organ harvesting; meanwhile, the Del Nido solution is one of the most frequently used cardioplegia solutions for pediatric cardiac surgery. Other solutions, such as the modified St. Thomas, Marshall, CRMB solution, and Custodiol N, have also been used clinically in recent years. The classification of myocardial preservation solutions is shown in Table 3 (Ref. [80,81]).

Studies by Kofler *et al*. [82] and data from the United Network for Organ Sharing indicate that using the UW solution for preserving donor hearts results in a significantly higher survival rate of transplant recipients than the HTK and Celsior solutions. The HTK solution, with its strong histidine buffering power, is considered superior for myocardial preservation and in protecting coronary artery endothelial function, as verified in heart transplantation animal models [83]. However, recent research suggests that preservation using the UW solution reduces organ ischemic necrosis, thereby enhancing recipient survival rates, surpassing the other two solutions [84,85]. Other preservation solutions are still being researched and require further clinical verification. The perfusate used for DCD hearts may require additional treatment or special protective agents, such as special or improved HTK solutions, to improve resistance to the warm ischemia injury suffered by DCD hearts before harvesting. Extracorporeal circulation perfusion machines may also evaluate real-time cardiac function and pretreatment. These machines use standard perfusion fluid and special nutrition and metabolic support fluids to optimize the state of the heart before transplantation. Del Nido cardioplegia can induce cardiac arrest and protect the myocardium but require longer recovery times. A meta-analysis by Tan *et al*. [86] found lower mortality rates using the del Nido cardioplegia than the HTK cardioplegia. There are also reports of the del Nido cardioplegic solution being administered to donor hearts immediately before transplantation; this assisted preservation strategy has the potential to reduce severe primary graft dysfunction in heart transplant recipients [87]. Good donor heart protection is the premise of long-distance safe organ transport; however, no evidence currently exists to show which myocardial preservation solution promotes the best preservation. Notably, attention to perfusion pressure and time is critical during perfusion. The recommended pressures are 100 mmHg before cardiac arrest and 40–50 mmHg thereafter, with a perfusion time of 8–10 minutes [88,89]. Furthermore, the perfusion fluid should be increased when the perfusion time is insufficient [83,90]. After the organ is harvested, it is necessary to thoroughly check whether any myocardial injuries, structural abnormalities, or coronary artery lesions have occurred. If any significant abnormalities are identified, further assessments should be performed to determine the extent of the damage and the potential impact on graft function.

Evaluation and Future Development of DCD Heart Transplantation

The complications of DCD heart transplantation include ischemic injury, PGD, and increased risk of rejection, which limit the widespread application of this technique. Ischemic injury, resulting from the warm ischemia during the circulatory arrest of the donor, is one of the most prominent causes of complications in DCD heart transplantation. Studies have shown that prolonged ischemia significantly increases the risk of PGD, a major contributor to early graft failure [91–93]. Moreover, PGD, characterized by severe hemodynamic instability and inadequate graft perfusion, remains a leading cause of morbidity and mortality in DCD heart transplant recipients [94]. However, despite the potential risks associated with warm ischemia, clinical data indicate that mortality in DCD recipients is lower than in DBD recipients, with risk-adjusted six-month survival rates of 94% and 90%, respectively ($p < 0.001$) [94].

Immunological complications, particularly acute rejection, are also prominent in DCD heart transplantations. The ischemic stress that DCD hearts undergo may alter the antigenic landscape of the graft, potentially leading to en-

hanced immunogenicity and a higher incidence of rejection episodes [95]. IRI enhances allograft immunogenicity by activating donor-derived dendritic cells (ADDCs), producing a heightened recipient immune response. This activation contributes to acute and chronic rejection. Indeed, a study demonstrated that treating donor hearts with MCI-186, a free radical scavenger, reduced ADDC activation and prolonged graft survival without immunosuppression [96].

Another critical issue in DCD heart transplantations is donor–recipient mismatch. Despite advancements in matching strategies, including the consideration of biochemical markers such as lactate levels and time-to-preservation, discrepancies in graft outcomes remain prevalent. Some recipients may experience superior outcomes even with suboptimal donor characteristics, while others suffer adverse outcomes despite favorable matching parameters [97,98]. The challenge lies in identifying reliable predictive biomarkers that can effectively gauge graft viability and potential for rejection. Current efforts focus on improving *ex vivo* perfusion techniques and monitoring molecular markers during organ preservation to enhance donor–recipient compatibility. Monitoring donor-derived cell-free DNA (dd-cfDNA) and gene expression profiles (GEPs) in recipients, Bui *et al*. [99] provided valuable insights into graft injury, demonstrating that elevated levels of dd-cfDNA and specific GEP patterns are associated with an increased incidence of acute rejection episodes in DCD heart transplant recipients.

Furthermore, exposing donor grafts to specific conditions before transplantation can modulate immune responses. For instance, transferring *ex vivo* expanded antigen-specific regulatory T-cells (iTregs) has shown promise in preventing allogeneic cardiac graft rejection. Indirect iTregs, induced by presenting specific MHC class I peptides on donor dendritic cells, were particularly effective in prolonging graft survival [100]. Additionally, advancements in gene editing and cellular therapy may present future strategies for reducing immunological rejection and enhancing graft resilience; however, these technologies remain in their infancy.

Ethical Controversies Faced by the DCD Heart Transplantation Scheme

Heart transplantation after circulatory death has now become a routine part of transplant programs in many countries, including the United States, Spain, Belgium, the Netherlands, and Austria. While many clinical practices have demonstrated that DCD heart transplantation can effectively maximize the use of organ resources, expand donor pools, and enhance the success of heart transplantation, these practices are often not permitted or accepted in many countries due to religious, ethical, and legal considerations. For instance, Spain permits two methods of DCD heart transplantation, Australia allows DPP with machine perfusion but not NRP, and Germany currently does not allow DCD [6,52,101]. The situation is more complex in the United States, with acceptance varying by state and even within individual hospitals [4,102,103]. Therefore, when considering the application of NRP, factors beyond national, religious, and moral concerns should be considered, such as the distance between the donor and recipient and the preservation and transportation of the donor heart. Rather than comparing which reperfusion method is superior, the focus should be on selecting the best option for patients in different scenarios.

The donor selection of DCD heart transplantation must adhere to the rules for deceased donors, ensuring no interventions occur before death is declared [80,104]. However, the exact definition of death in DCD heart donation varies from country to country, and it is very important to define the precise time of death [4,105]. The decision of when to stop resuscitation intervention and declare death is sensitive, and a strong ethical and legal framework is required to guide medical professionals. In the United States, death is initially declared when circulatory arrest occurs (absence of pulse or a flat arterial line) [28]. Once organ donation is specified, a 5-minute observation period is established to rule out the possibility of spontaneous recovery. If no signs of life are observed, death is declared a second time [29]. Only after the second declaration of death can the transplant team take over the donation process and initiate the organ procurement procedure. U.S. medical institutions follow these basic principles but implement their own DCD policies [106]. The observation window after WLST varies from 60 to 120 minutes, and only those declared dead during this period can proceed to organ procurement; otherwise, the patient continues to receive treatment and is not eligible for organ donation. The time interval for death declaration varies significantly between states in the United States: Some states require a 5-minute ‘stand-off’ period, while others may extend this to 20 minutes. European countries, such as the Netherlands and Belgium, adopt stricter time standards, requiring a 5-minute ‘no-touch’ period to ensure the heart is fully arrested and cannot be restored. In China, the ‘stand-off’ period in DCD organ transplantation typically ranges from 2 to 5 minutes after WLST. In some high-level hospitals, a longer period may be required to ensure the irreversibility of the donor’s death.

Hence, the definition of death in the context of DCD remains a subject of ongoing debate. Death is generally defined as irreversible, but the reinitiation of blood circulation during reperfusion challenges this definition. NRP reestablishes circulation to organs, including the lungs, liver, and kidneys, but if blood flow to the brain is not fully blocked, then brain perfusion may occur. In such cases, brain function in the donor may be restored, which contradicts the “dead donor rule” and provokes strong opposition from supporters of DBD. Thus, surgical measures, such as

clamping the carotid and subclavian arteries, are often employed to prevent brain perfusion during NRP. Meanwhile, a recent study from Spain reported anencephalic blood perfusion during NRP [107]. Nevertheless, technical uncertainties remain, as incomplete isolation of the blood flow to the brain could lead to unnoticed perfusion of distal cerebral vessels. These technical challenges have led to legal and ethical concerns surrounding NRP in certain regions.

The ISHLT 2022 consensus statement recommended that DCD and NRP be approached with caution, in line with local guidelines, and that DCD be conducted in an ethically permissible manner, with due consideration of the ethical principles involved in organ donation [108,109]. In any case, the introduction of DCD programs must comply with local laws and regulations.

Conclusions

In conclusion, DCD heart transplantation offers a promising solution to the critical shortage of donor hearts. However, to ensure the safe and effective implementation of DCD heart transplantation globally, future efforts should focus on fostering multicenter clinical trials and establishing robust frameworks for international collaboration. Meanwhile, standardizing key aspects such as donor selection criteria, definitions of warm ischemic time, and ethical protocols—including death declaration procedures and NRP safeguards—requires coordinated action among transplant centers, regulatory agencies, and bioethics committees. Collaborative networks and shared data registries are essential to harmonize practices across institutions and regions. In parallel, policy development should prioritize creating adaptable yet ethically grounded guidelines that respect regional legal and cultural contexts, while promoting innovation in organ preservation technologies.

Author Contributions

HL, XM, YL, and XW contributed to the conception and design of the review. HL, XM, JL, and YZ drafted the manuscript after summarizing and analyzing the data. YL and XW critically reviewed and revised the manuscript for important intellectual content. All authors have read and agreed to the published version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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