Successful Recovery of Cardiac Function Following 20 min of a No-touch Period in a Donation After Circulatory Death: A Case Report

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Background. Withdrawal of life-sustaining therapy (WLST) performed in the circulatory determination of death (DCD) donors leads to cardiac arrest, challenging the utilization of the myocardium for transplantation. The rapid initiation of normothermic regional perfusion or extracorporeal membrane oxygenation after death helps to optimize organs before implantation. However, additional strategies to mitigate the effects of stress response during WLST, hypoxic/ischemic injury, and reperfusion injury are required to allow myocardium recovery. **Methods.** To this aim, our team routinely used a preconditioning protocol for each DCD donation before and during the WLST and after normothermic regional perfusion/extracorporeal membrane oxygenation. The protocol includes pharmacological treatments combined to reduce oxidative stress (melatonin, *N*-acetylcysteine, and ascorbic acid), improve microcirculation (statins), and mitigate organ's ischemic injury (steroids) and organ ischemia/reperfusion injury (remifentanil and sevoflurane when the heart is available for transplantation). **Results.** This report presents the first case of recovery of cardiac function, with the only support of normothermic regional reperfusion, following 20 min of a no-touch period and 41 min of functional warm ischemic time in a DCD donor after the preconditioning protocol. **Conclusions.** Our protocol seems to be effective in abolishing the stress response during WLST and, on the other hand, particularly organ protective (and heart protective), giving a chance to donate organs less impaired from ischemia/reperfusion injury.

(*Transplantation* 2024;00: 00–00).

INTRODUCTION

Controlled donation after circulatory determination of death (DCD) represents a key strategy to increase the availability of organs and address the growing demand for transplantation.[1] However, the withdrawal of life-sustaining therapy (WLST) performed in DCD donors leads to cardiac arrest, challenging the utilization of the ischemic myocardium for transplantation.[2] The difficulty of using hearts for transplantation after DCD is greater in Italy, considering the required 20 min of "no-touch period" to certify death before organs can be retrieved, the longest among European countries performing DCD.[1]

Received 7 August 2023. Revision received 2 December 2023.

Accepted 8 December 2023.

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The authors declare no funding or conflicts of interest.

P.Z. participated in study design. All authors contributed in data collection and interpretation, edited the article, and approved the article for submission. P.Z. and F.L. participated in article writing.

The procedure of withdrawal of life-sustaining therapy is disciplined by our ethical committee (May 2022) and was performed after obtaining written consent from the nearest family member (ie, the wife) in accordance with the donor's wishes. All the clinical maneuvers were performed according to no maleficence and beneficence principles toward the donor and the recipient and within the existing national guidelines on circulatory determination of death donation.

All data generated or analyzed in this case report are included in this article. Further inquiries can be directed to the corresponding author.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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ISSN: 0041-1337/20/0000-00

DOI: 10.1097/TP.0000000000004940

Three phases of myocardium exposure to injury can be defined in DCD transplantation: warm hypoxic/ischemic injury from WLST to death; warm ischemic injury during the asystolic no-touch period; and ischemic/reperfusion injury during normothermic regional reperfusion (NRP) and organ cold storage or ex vivo organ perfusion, transportation, and implantation.[3] The rapid initiation of NRP with aortic ballooning after death helps to minimize the impact of warm ischemic time and optimize the abdominal donor organs before implantation.[4] However, additional strategies to mitigate the effects of stress response during the WLST, hypoxic/ischemic injuries, and reperfusion injuries could be used to facilitate the recovery of myocardium.[4] To this aim, in the Department of Anesthesiology and Critical Care of Treviso Regional Hospital, a preconditioning protocol has been defined and is routinely adopted for DCD donation before and during the WLST and after NRP/extracorporeal membrane oxygenation (ECMO) reperfusion. The protocol includes pharmacological treatments combined to reduce oxidative stress (*N*-acetylcysteine, melatonin, and ascorbic acid), improve microcirculation (statins), and mitigate organ's ischemic injury (steroids) and organ ischemia/reperfusion injury (remifentanil; Figure 1). These drugs have been combined for the first time in this clinical protocol since, according to the literature, their benefits were individually studied. No clinical studies have been reported about their combination. This report presents the first case of a successful recovery of cardiac function, with the only support of NRP, following 20 min of a no-touch period and 41 min of functional warm ischemic time in a DCD donor after the preconditioning protocol.

CASE PRESENTATION

In April 2023, a 62-y-old patient was admitted to the cardiac intensive care unit in postanoxic coma after 40 min of cardiac arrest caused by ventricular fibrillation for mitral valve prolapse and fibrosis of the papillary muscles with a moderate insufficiency.[5]

Following admission, several clinical, neurophysiological (electroencephalogram, somatosensory evoked potentials), and neuroradiological (cerebral computed tomography scan and brain MRI) evaluations defined a severe neurological prognosis. The family refused a severe disability condition, in accordance with the will expressed in life of their relative, and understood the appropriateness of starting WLST, accepting the opportunity to donate the patient's organs. According to the protocol approved by the ethics committee, the WLST was anticipated by a phase sedation to prevent distress at the end of life, as recommended by the Italian Society of Anesthesia and Intensive Care Guidelines.[6]

The preconditioning protocol started as soon as the next of kin were informed about medical decisions on WLST and advanced the willingness to donate (for a total of 3 d). Despite a pulmonary contusion and a previous pseudomonas infection successfully treated, the possibility of donating lungs was considered, together with liver and kidneys. The heart, even if the patient was younger than 65 y, was not considered viable for transplantation because of the previous damage history.

The patient was subjected to a pronation cycle to improve the perfusion–ventilation coupling of the lung atelectatic area. During this maneuver, a second short cardiac arrest occurred because of an endotracheal tube obstruction. The patient was resuscitated and repositioned supine; vital signs were within the normal range, and the high-sensitive troponin T curve rose slightly, reaching 57 ng/L.

On the day of WLST, femoral vessel cannulation was performed, and a heparin bolus of 300 IU/kg was administered after sedation started near the agonic phase (**Video S1**). The agonic phase lasted 16 min (**Video S2**). After the declaration of death and 20 min of no-touch period, cardiac surgeons inserted ECMO cannulas through femoral introducers (**Figure S1 and Table S1, SDC,** http://links.lww.com/TP/C976). After NRP, a vascular complication in the femoral artery site occurred, preventing the correct positioning of the intra-aortic balloon. As a consequence, after 12 min from the beginning of reperfusion,

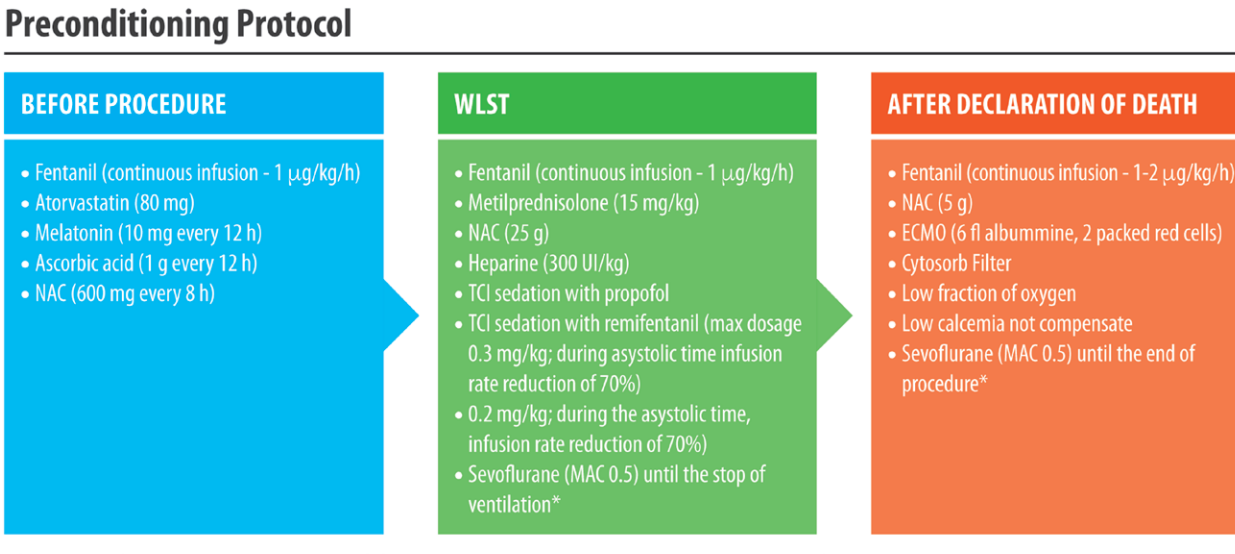

FIGURE 1. Preconditioning protocol phases and administered drugs. MAC, minimum alveolar concentration.

we assisted in an accidental, unexpected resumption of cardiac function without any inotropic support (**Video S3**). Due to this unexpected condition, an emergent median sternotomy was performed to quickly isolate and exclude supra-aortic trunk circulation, according to our national guidelines on DCD donation. Blood chemistry tests showed a rapid improvement in lactic acid clearance, no significant increases in aspartate transaminase and alanine transaminase parameters, and a slight increase in high-sensitive troponin T (Table 1). After 30 min, the body was ready to be weaned off from ECMO, which was maintained to facilitate the removal of the lungs, liver, and kidneys. These organs were successfully transplanted with early graft and functional recovery in the recipients.

DISCUSSION

We report the first case of recovery of cardiac function without heart surgery maneuvers following 20 min of a no-touch period in a DCD donor. In this patient, a preconditioning protocol was applied to minimize the stress response before and during the WLST phase, giving a more dignified time of death and huge benefits for the organ recipient, thanks to preventing and reducing organ ischemia damage. Within the preconditioning protocol, the *N*-acetylcysteine (NAC) treatment is used along all 3 phases (Figure 1). NAC is a synthetic derivative of the amino acid L-cysteine, which has been extended to treat ischemia–reperfusion cardiac injury.[7,8] NAC has been shown to potentiate the vasodilator effects of nitroglycerin and angiotensin-converting enzyme inhibitors and to reduce myocardial oxidative stress, thanks to its well-known antioxidant activity (glutathione replenishment and reactive oxygen species scavenging).[9] Moreover, NAC is also a potent antithrombotic drug.[10] The preconditioning protocol also provides the administration of statin[8] to improve microcirculation and inhibit the release of inflammatory cytokines and mitochondrial reactive oxygen species,[11] melatonin to reduce oxidative stress and myocardial apoptosis,[12] and ascorbic acid to prevent apoptosis and inflammation.[13] Before the warm ischemia, a steroid bolus was administered to attenuate ischemic injury to the organ.[14] Among opioids, remifentanil is protective against ischemia–reperfusion injury by lowering hypoxia-mediated protein carboxylation and limiting inflammatory reactions.[15]

Target-controlled infusion is a widely used computer-controlled method for rapidly achieving and maintaining a stable concentration at the effect site of anesthetic drugs (ie, Propofol and Remifentanil) based on physiological parameters, such as the patient's age, weight, height, and sex during total intravenous anesthesia.[16,17] According to our protocol, the estimated concentration at the effector site (Ce) of Propofol was targeted to >1.5 μg/mL and that of remifentanil to >1.5 ng/mL, aiming to suppress the sympathetic activity and guarantee a dignitary (and ethically approved) agonic phase.

Sevoflurane is added to the protocol when the myocardium is available for transplantation based on increasing evidence suggesting its role in reducing myocardial ischemia–reperfusion injury.[18] These properties, combined with the safety profile, low cost, and ease of administration, make the preconditioning protocol a potential bullet for reducing ischemia–reperfusion damage in solid organ

TABLE 1.
Blood chemistry test and blood gas analysis

	08:15	09:31	09:34	10:06	10:15	10:24	10:42	11:08
Parameters (normal lab value)	**Pre–agonic phase**	**Agonic phase**		**Asystolic no-touch period**		**ECMO perfusion**		
pH (7.35–7.45)	7.57	7.46	7.44	7.17	7.07	7.45	7.54	7.6
pCO_2 (35–45 mm Hg)	35	43	46	92	71	56	24	26
pO_2 (80–100 mm Hg)	100	36	29	19	75	384	309	232
Na (136–145 mEq/L)	138	140	140	136	134	155	142	144
K (3.4–4.5 mEq/L)	3.5	3.3	3.6	4.1	5.1	3.3	3.6	3.5
Cl (98–107 mEq/L)	108	105	103	101	97	106	103	103
Ca (1.15–1.29 mg/dL)	1.1	1.02	1.07	0.97	1	0.8	0.89	0.82
Hct (40%–52%)	24	24	25	26	24	23	23	
Glu (74–109 mg/dL)	116	122	119	109	453	210	229	236
Lac (0.5–2.2 mmol/L)	0.9	1	1.2	2.7	9.5	9.2	8.6	8.3
Hb (14–18 g/dL)	9.3	9.4	9.6	9.4	9.1	9.2	9.3	10
O_2Hb (95%–98% Hb_{tot})	96.9	55.4	35.7	10.2	89.3	98.9	97.9	97.5
sO_2 (40%–97%)	98.8	56	36.2	10.3	90.8	100.4	100.1	100.3
BE (0–3 mmol/L)	10.1	6.8	7	5.3	-9.5	14.9	-2	4.4
Creatinine (0.67–1.17 mg/dL)	0.53					0.37	0.51	0.41
AST (4–40 U/L)	51					42	38	35
ALT (4–41 U/L)	31					21	22	20
cTnT-hs (0–14 ng/L)	81					49	57	43
CK-MB (0–3.8 ng/L)	1.2					0.8	1.5	1.1
LDH (135–214 mU/mL)	328					264	277	242
CPK (20–180 U/L)	33					24	27	23

ALT, alanine transaminase; AST, aspartate transaminase; CK-MB, creatine kinase-myocardial band; CPK, creatinine phosphokinase; cTnT-hs, high-sensitive troponin T; ECMO, extracorporeal membrane oxygenation; Glu, glucose; Hb, hemoglobin; Hct, hematocrit; Lac, lactic acid; LDH, lactate dehydrogenase.

transplantation. For instance, this patient did not donate a heart because of primitive damage. Notably, the same protocol led to the first heart transplantation in another patient a few weeks before, discussed elsewhere.[19] In this patient, cardiac surgery maneuvers were adopted to resuscitate the heart (cross-clamping of aorta, infusion with cardioplegic C Buckberg solution, insertion of a right pulmonary vein vent, clamping of epiaortic vessels, and then removing of the aortic clamp and weaning from cardiopulmonary bypass).[19]

The outstanding results described in this report suggest that the preconditioning protocol should be further investigated to optimize the DCD resource, in particular, to elucidate which of the drugs adopted in the protocol has the highest clinical relevance in reducing organ damage after ischemia–reperfusion injury, and to define the better timing to start this protocol. Moreover, after the validation of this approach, the preconditioning therapy could be extended to patients following ischemia to protect organs from oxidative stress damage.

ACKNOWLEDGMENTS

Editorial assistance was provided by Simonetta Papa, PhD, Valentina Attanasio, and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Zambon Italia Srl (Italy).

REFERENCES

1. Domínguez-Gil B, Haase-Kromwijk B, Van Leiden H, et al; European Committee (Partial Agreement) on Organ Transplantation. Council of Europe (CD-P-TO). Current situation of donation after circulatory death in European countries. *Transpl Int*. 2011;24:676–686.
2. Shemie SD, Torrance S, Wilson L, et al. Heart donation and transplantation after circulatory determination of death: expert guidance from a Canadian consensus building process. *Can J Anaesth*. 2021;68:661–671.
3. Kearns MJ, Miller SD, Cheung A, et al. A rodent model of cardiac donation after circulatory death and novel biomarkers of cardiac viability during ex vivo heart perfusion. *Transplantation*. 2017;101:e231–e239.
4. James L, LaSala VR, Hill F, et al. Donation after circulatory death heart transplantation using normothermic regional perfusion: the NYU protocol. *JTCVS Tech*. 2023;17:111–120.
5. Basso C, Perazzolo Marra M, Rizzo S, et al. Arrhythmic mitral valve prolapse and sudden cardiac death. *Circulation*. 2015;132:556–566.
6. Malacarne P, Livigni S, Vergano M, et al. Le cure di fine vita e l'anestesista rianimatore: raccomandazioni siaarti per l'approccio alla persona morente. (End-of-life care and the anesthetist: siaarti recommendations for the approach to the dying person). Available at https://www.sicp.it/wp-content/uploads/2018/12/148_DocSIAARTI_FIneVita_26618.pdf.
7. Bartekova M, Barancik M, Ferenczyova K, et al. Beneficial effects of N-acetylcysteine and N-mercaptopropionylglycine on ischemia reperfusion injury in the heart. *Curr Med Chem*. 2018;25:355–366.
8. Samuni Y, Goldstein S, Dean OM, et al. The chemistry and biological activities of N-acetylcysteine. *Biochim Biophys Acta*. 2013;1830:4117–4129.
9. Raghu G, Berk M, Campochiaro PA, et al. The multifaceted therapeutic role of N-acetylcysteine (NAC) in disorders characterized by oxidative stress. *Curr Neuropharmacol*. 2021;19:1202–1224.
10. Martinez de Lizarrondo S, Gakuba C, Herbig BA, et al. Potent thrombolytic effect of N-acetylcysteine on arterial thrombi. *Circulation*. 2017;136:646–660.
11. Gavazzoni M, Gorga E, Derosa G, et al. High-dose atorvastatin versus moderate dose on early vascular protection after ST-elevation myocardial infarction. *Drug Des Devel Ther*. 2017;11:3425–3434.
12. Lan H, Su Y, Liu Y, et al. Melatonin protects circulatory death heart from ischemia/reperfusion injury via the JAK2/STAT3 signalling pathway. *Life Sci*. 2019;228:35–46.
13. Gori F, Fumagalli J, Lonati C, et al. Ascorbic acid in solid organ transplantation: a literature review. *Clin Nutr*. 2022;41:1244–1255.
14. Martens A, Boada M, Vanaudenaerde BM, et al. Steroids can reduce warm ischemic reperfusion injury in a porcine donation after circulatory death model with ex vivo lung perfusion evaluation. *Transpl Int*. 2016;29:1237–1246.
15. Lewinska A, Adamczyk-Grochala J, Bloniarz D, et al. Remifentanil preconditioning protects against hypoxia-induced senescence and necroptosis in human cardiac myocytes in vitro. *Aging (Albany NY)*. 2020;12:13924–13938.
16. Al-Rifai Z, Mulvey D. Principles of total intravenous anesthesia: practical aspects of using total intravenous anesthesia. *BJA Educ*. 2016;16:276–280.
17. Vandemoortele O, Hannivoort LN, Vanhoorebeeck F, et al. General purpose pharmacokinetic-pharmacodynamic models for target-controlled infusion of anaesthetic drugs: a narrative review. *J Clin Med*. 2022;11:2487.
18. Yang J, Tang L, Zhang F, et al. Sevoflurane preconditioning promotes mesenchymal stem cells to relieve myocardial ischemia/reperfusion injury via TRPC6-induced angiogenesis. *Stem Cell Res Ther*. 2021;12:584.
19. Gerosa G, Zanatta P, Angelini A, et al. Overcoming the boundaries of heart warm ischemia in donation after circulatory death: the Padua case. *ASAIO J*. [Epub ahead of print February 9, 2024]. doi: 10.1097/MAT.0000000000002141