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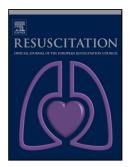Please cite this article as: Villares José Miguel Pérez, Rubio Juan José, Río Francisco del, Miñambres Eduardo.Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion.*Resuscitation* http://dx.doi.org/10.1016/j.resuscitation.2017.05.030

Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion

José Miguel Pérez Villares[1], Juan José Rubio[2], Francisco del Río[3], Eduardo Miñambres[4].

[1]Transplant Coordination Unit & Service of Intensive Care. University Hospital Virgen de las Nieves. Granada. SPAIN

[2]Transplant Coordination Unit & Service of Intensive Care. University Hospital Puerta de Hierro. Madrid. SPAIN

[3]Transplant Coordination Unit & Service of Intensive Care. University Hospital Clinico San Carlos. Madrid. SPAIN.

[4]Transplant Coordination Unit & Service of Intensive Care. University Hospital Marqués de Valdecilla-IDIVAL. School of Medicine, University of Cantabria, Santander. SPAIN.

Corresponding author: Dr. Eduardo Miñambres. Transplant Coordination Unit & Service of Intensive Care. Hospital Universitario Marqués de Valdecilla, Avenida Marqués de Valdecilla s/n, E-39008 Santander, Spain.

Tel.: +34–942–203304

Fax: +34–942–315306

E-mail: eminambres@yahoo.es

Abstract

Aim: The use of abdominal normothermic regional perfusion (nRP) and premortem interventions in controlled donation after circulatory death (cDCD) may represent a significant advance to increase the number and quality of grafts recovered in cDCD. The main limitation for the widespread acceptance of nRP in cDCD is the concerns of restoring circulation to the brain once death has been declared should the thoracic aorta not be adequately blocked.

Methods: We describe and validate a specific methodology to ensure an appropriate blocking of the thoracic aorta in a multicenter study using this technique.

Results: A total of 78 procedures with premortem cannulation and abdominal nRP were performed in four different hospitals. No case of heart or brain resuscitation was observed after nRP

Conclusion: The use of premortem interventions before nRP and the aortic occlusion balloon may increase the number of grafts recovered in cDCD. Our proposed methodology avoids the ethical problem of resuscitation by guaranteeing that circulation to the heart and brain is not restored after nRP

Keywords: controlled donation after circulatory death; cerebral resuscitation; normothermic regional perfusion

<u>Introduccion</u>

Controlled donation after circulatory death (cDCD) has expanded significantly over the last decade. Nevertheless, the unpredictable consequences of warm ischemic injury, which characterizes cDCD, result in a reluctance to use organs from these donors and lower patient and graft survival, particularly among liver recipients[1]. In recent years,

there has been growing interest in using abdominal normothermic regional perfusion (nRP) with extracorporeal membranous oxygenation (ECMO) devices to restore blood flow to the abdominal cavity after death in cDCD[2]. This strategy may restore cellular energy substrates and as organ function can be assessed prior to transplantation, better grafts may be selected, compared to current cDCD transplantation[3]. nRP also transforms an urgent recovery procedure into an elective one, an advance that could reduce organ damage and losses due to surgical events.

Ethical concerns about the use of abdominal nRP and premortem interventions in cDCD have been aired[4], including the possibility of resuscitating the patient after death declaration.

To resolve ethical challenges in a methodological manner, the facts of the situation must be analyzed. The ethical problem of resuscitation could be avoided if an nRP procedure to guarantee the absence of cardiac or cerebral resuscitation is developed.

The legal framework regulating cDCD varies significantly among different countries. In some places, premorten cannulation is forbidden, while in others it can performed with the consent of the patient or his family.

According to the Spanish regulatory framework, specific informed consent must be obtained for any premortem interventions, immediately after consent for organ donation has been obtained from the legal representatives of the potential donor (2 separate consents must be obtained, one for organ donation and the other for premortem interventions).

We describe and validate for the first time a specific methodology to ensure appropriate blocking of the thoracic aorta during nRP in four Spanish centers.

Methods. New proposal to avoid donor resuscitation

This is a multicenter retrospective review of all actual cDCD procedures performed with premortem cannulation and nRP at four Spanish centers from the start of the programmes (2014) to January 2017.

cDCD was considered in patients < 75 years, in whom the decision had been made to withdraw life-sustaining treatment (WLST) on the grounds of futility of further care. The common protocol to avoid donor resuscitation during nRP is described below.

1. Informed consent

Specific informed consent for premortem interventions, consisting of the administration of heparin (500-600 IU/kg) and cannulation of femoral vessels prior to the WLST, was obtained.

2. Cannulation of the femoral vessels

The femoral artery and femoral vein were cannulated surgically or percutaneously using the Seldinger technique, with adequate sedation and analgesia.

3. Aortic occlusion catheter

An aortic occlusion balloon was placed through the contralateral groin, in order to relegate preservation measures to the abdominal cavity during nRP. We used standard commercial devices as aortic occlusion balloon. Before WLST, the aortic occlusion balloon was filled for just 4 seconds, in order to confirm that pressure from the arterial femoral cannula disappeared while the left wrist line was maintained (Figure 1A), ensuring that the thoracic aorta was adequately blocked. The balloon was then immediately emptied. The filling volume was recorded as the minimum volume to be used to block the aorta during nRP.An X-ray or fluoroscopy view was obtained before WLST to ensure the correct positioning of the catheter.

Two arterial lines, one from the femoral arterial cannula and the other from the left radial artery, were monitored throughout the procedure.

4. Withdrawal of life-sustaining therapy

WLST was performed in the ICU or in the operating room. Relatives were allowed to be with the potential donor throughout the whole process.

5. Determination of death

The absence of circulation was defined when there was no pulsatile wave form in both arterial lines. A 5-minute no-touch period after the circulatory arrest was mandatory for death to be declared. The bispectral index was monitored before and after WLST to ensure there was no cerebral activity after nRP.

6. Balloon filling and start of normothermic regional perfusion

After death was certified and nRP was started, arterial pressure from the left radial artery disappeared with adequate blocking of the thoracic aorta, while the pressure from the femoral arterial cannula was maintained, but pressure was continuous rather than pulsatile because it was provided by the ECMO device (see Figure 1B). A continuous pressure > 60-65 mmHg was maintained.

7. Detection of catheter malfunction or incorrect positioning

If flow was detected in radial line, nRP was immediately stopped and correct positioning or filling of the catheter was checked. The nRP was then reinitiated after a no-touch period of 5 minutes.

8. Normothermic regional perfusion monitoring

The abdominal nRP objective was to maintain a pump flow of 2.2-2.4 L/min. Continuous pressure > 60-65 mmHg was maintained in the femoral arterial cannula. Temperature was maintained at 37ºC, bicarbonate was always administered just after

nRP had started, with the aim of maintaining pH between 7.35-7.45 and hematocrit > 25%.

Blood samples from the ECMO device were obtained just after starting nRP and at least every 30 minutes. Biochemistry, serum lactate levels and hematocrit were analyzed. If alanine transaminase or aspartate transaminase levels at 30 or 60 minutes after the initiation of nRP were > 4 times the normal values, the liver was discarded even if the macroscopic appearance was normal.

Results

A total of 78 cDCD procedures were performed (Table 1). We only included those type III donors whose grafts were recovered with nRP. In three cases, premortem cannulation was not possible and the organs were finally recovered with a rapid recovery (RR) technique.

Organ recovery and transplantation activity at the individual centers are shown in Table 2. A detailed description of the outcomes of these grafts is beyond the scope of this letter, which aims only to explain the technical aspects of nRP management. No case of heart or brain resuscitation was observed. In 4 cases, just after nRP had started, the arterial pressure from the left radial artery was maintained as continuous pressure. Consequently, the ECMO device was immediately stopped, the aortic balloon checked (usually the balloon needed to be inflated more), and a 5-minute no-touch period was observed before nRP was restarted.

Discussion

The rate of cDCD has increased in recent years all over the world[1]. However, cDCD has been associated with limited organ utilization and worse post-transplant outcomes

compared to donation after brain death, especially in liver transplantation[1], where an increased incidence of primary non-function and ischemic cholangiopathy have been observed[1,3]. However, in nearly all reported procedures, organ recovery was performed with RR surgery.

Ethical concerns about the use of abdominal nRP and premortem interventions in cDCD have been raised, including the possibility of resuscitating the patient after death declaration[5]. This can occur when the aorta is not adequately blocked, e.g. due to incorrect positioning or inadequate filling of the aortic balloon, which allows the resumption of brain circulation. Surprisingly, no procedure to minimize such a dangerous possibility has been published. Cyanosis in the upper torso, upper extremities and head occurs after several minutes without thoracic and head perfusion. However, these are very late clues for diagnosing a failure to block the thoracic aorta. In our view, this ethical concern, which is the main limitation for the acceptance of nRP in cDCD is solved with our proposal.

To our knowledge, this is the first time a procedure has been applied to minimize this risk and this type of proposal has not been previously described in the medical literature. Our protocol is easy and safe and can help to immediately diagnose failure, in order to prevent donor resuscitation

The theoretical possibility of resuscitating the potential cDCD donor after declaration of death has limited the widespread acceptance of nRP. Thus, in some countries nRP is performed without previous cannulation[5] and functional warm ischemic time (FWIT) increases by about 10 minutes. The aortic occlusion balloon offers the advantage of permitting the initiation of nRP immediately after the no-touch period, whereas aortic clamping imposes a delay because it can be deployed only after a sternotomy. The extra time needed for abdominal laparotomy, thoracic aorta clamping, and femoral artery and

vein cannulation could exceed the upper time limit for liver acceptance. In current practice FWIT > 30 minutes is considered a contraindication for liver acceptance. Therefore, the use of premortem interventions before nRP and the aortic occlusion balloon decreases FWIT and may increase the number of grafts recovered in cDCD. The optimal duration of abdominal nRP in cDCD is to be determined. In our cDCD protocol, abdominal nRP is maintained usually 90-120 minutes. This allows to restore cellular energy substrates and to assess the suitability of the grafts[6].

In summary, abdominal nRP may represent a significant advance in increasing the number of grafts recovered from cDCD. We describe and validate for the first time a specific methodology to ensure appropriate blocking of the thoracic aorta during nRP Our proposal avoids the ethical problem of resuscitation and guarantees the absence of cardiac or cerebral resuscitation. Further studies are needed to confirm our findings.

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Figure 1.

A. Aortic occlusion catheter in the correct position with the balloon filled with radiopaque contrast. The femoral pulse taken in the ECMO cannula disappears when the balloon is filled while the radial pulse is maintained. The complete disappearance of the femoral pulse indicates the minimum filling balloon volume.

B. If the aortic occlusion catheter is correctly positioned, the femoral cannula shows a non-pulsatile pressure while there is neither radial artery pressure nor oxygen saturation (right). If the balloon is not completely full or is too advanced, non-pulsatile pressure will be detected in both femoral and radial arteries (left)
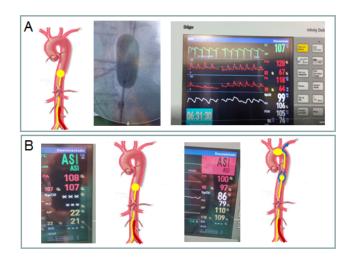
Table 1. Donor characteristics

Total donors: 78
Age: 59 years (50-67)
Gender (male): 54 (69%)
Cause of death: haemorrhagic cerebrovascular accident 14 (18%)
Ischemic cerebrovascular accident   14 (18%)
Traumatic brain injury   7 (9%)
Cerebral anoxia   25 (32%)
Terminal respiratory failure   10 (13%)
Others   8 (10%)
Use of vasoactive drugs: 34 (44%)
Time WLTS-CA (min): 17 (12-22)
ICU stay (days): 6 (4-10)

Data expressed in median (25th to 75th interquartile range). Gender, cause of death and use of vasoactive drugs: absolute number (%). WTLS: withdrawal of life-sustaining therapy. CA: cardiac arrest. ICU: intensive care unit

	Actual cDCD donors	kidneys	livers	lungs[1]	pancreas
Hospital San Carlos	17	28	2	3[2]	
Hospital Puerta de Hierro	8	12	5	2[3]	
Hospital Virgen de las Nieves	21	29	9		
Hospital Marques de Valdecilla	32	47	12	12[4]	1
Total	78	116	28	17	1

Table 2. Individual center data on donors subject to nRP and organ transplant activity. A total of 2.1 organs per donor (162/78) were recovered and transplanted
[1]Number of grafts transplanted; [2]One double lung transplant and one single transplant; [3]One bilateral lung transplant; [4]Six bilateral lung transplants