Mobile Extracorporeal Membrane Oxygenation Teams for Organ Donation After Circulatory Death

Maria Adele Figini[a,*], David Paredes-Zapata[b], Eva Oliver Juan[c], and Davide Alberto Chiumello[a]

[a]Department of Anesthesia and Intensive Care Unit, ASST Santi Paolo e Carlo, Milano, Italy; [b]Donation and Transplantation Coordination Unit, Hospital Clinic, Barcelona, Spain; and [c]Transplantation Unit, Hospital de Bellvitge, Barcelona, Spain

ABSTRACT

The shortage of available organ donors is a significant problem worldwide, and various efforts have been carried out to avoid the loss of potential organ donors. Among them, organ donation from cardiocirculatory deceased donors (DCD), in which withdrawal of life-sustaining therapies is ongoing (Maastricht type III donors), is one emerging strategy. Thanks to the latest advances in transplantation and organ preservation, such as normothermic regional perfusion (NRP), ex vivo perfusion techniques, and good organization and communication among prehospital care providers, emergency departments, intensive care units, and transplantation units, DCD is rapidly increasing; it's estimated that it will increase the number of donations of lungs and splanchnic organs by more than 40%.

Although Maastricht type II DCD requires a 24/7 available experienced extra corporeal membrane oxygenation (ECMO) team in the institution, Maastricht DCD type III could be organized in secondary care and spoke hospitals without in loco ECMO facilities for NRP. This article analyses a potential mobile team organization based on the hub-and-spoke model, which already exists and functions in Italy, by estimating the dimension of the controlled DCD phenomenon in Italy, coordination requirements, costs, personnel training, and education, and reporting a single center experience in Milan, Italy.

TRANSPLANTATION is for many diseases the only lifesaving therapy; in some cases, it represents the only opportunity to return to an acceptable quality of life.

Although transplantation activity is increasing worldwide, the growing request for organs for transplantation is mismatched with the insufficient number of available donors, mainly because of the change, in recent years, of the profile of the donors: from traumatic cause of death to cerebrovascular cause of death and from young people dying in traffic accidents to older patients with multiple comorbidities but without a frank contraindication to organ donation. The adoption of the so-called expanded criteria donors has become a common clinical practice [1], while recently, thanks to the major opportunities offered by new technologies, donation after circulatory death (DCD; Fig 2) has emerged throughout the last decade as a new possibility, with a growing body of evidence of favorable transplantation outcome.

Controlled DCD or Maastricht Category III DCD (awaiting cardiac or circulatory death) is conceived in patients for whom circulatory death occurs after a planned withdrawal of life-sustaining therapies (WLST), mainly cardiorespiratory support [2] (Fig 1). Cardiac arrest is expected, and the medical decision of WLST is taken in a defined and multidisciplinary approach, consistent with local and national legal requirements, by the clinical team together with the family when further treatment is considered futile.

The number of organs recovered and transplanted through DCD is increasing in Europe, although it remains lower compared with donation after brain death (DBD). In a recent study on DCD by the Council of Europe [3], a survey of 27 participating countries was conducted, and only 10 of them confirmed any DCD activity, the highest being described in Belgium, the Netherlands, the United Kingdom (mainly controlled), France, and Spain (mainly uncontrolled). In some

*Address correspondence to Maria Adele Figini, ASST Santi Paolo e Carlo, Presidio San Paolo, via di Rudinì 8, 20142, Milan, Italy. Tel: +39 02 81844476; Fax +39 02 50323137. E-mail: maria.figini@asst-santipaolocarlo.it

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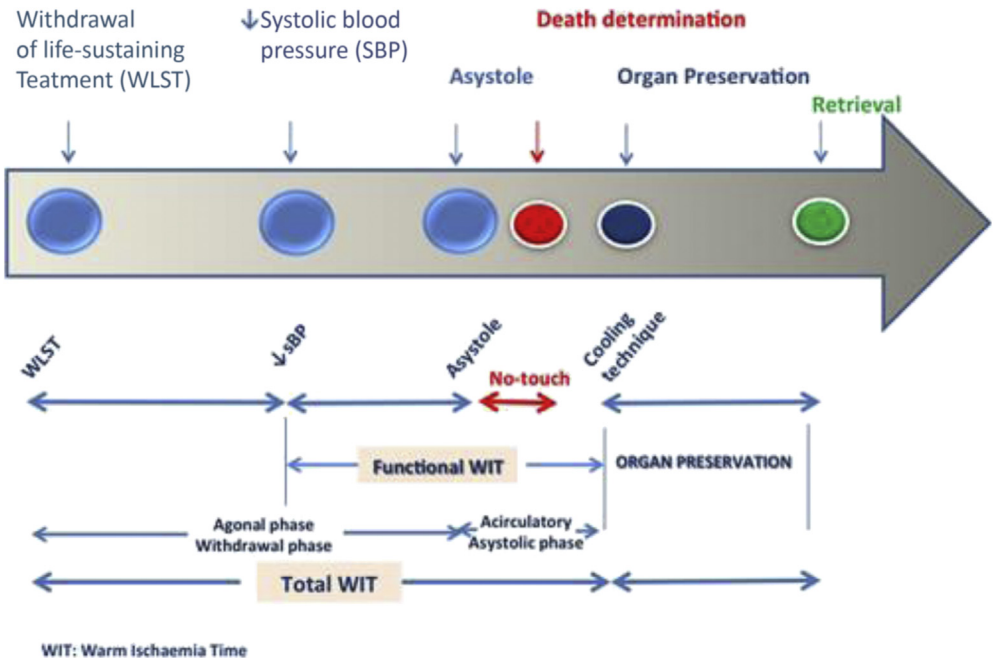

Fig 1. Controlled cardiocirculatory deceased donors process [39]. Functional warm ischemia time (WIT) starts when SBP is $\leq$ 50 mm Hg or $\leq$ 60 mm Hg. No-touch period: 2 minutes to 20 minutes.

countries, DCD is prohibited by law, whereas the so-called "no-touch period," defined as the time between the cessation of circulation and respiration and the determination of death by law, ranges from 5 minutes (Spain, United Kingdom, France, the Netherlands, and Belgium) to 20 minutes (Italy). According to these substantial differences, the super-rapid laparotomy and sternotomy with direct arterial cannulation or extra corporeal membrane oxygenation (ECMO) are procedures gaining predominance to allow multiorgan recovery from DCD donors.

In Italy, controlled donation after circulatory death (cDCD) has been previously considered unadvisable [4], mainly because Italian law demands an absence of ECG activity (the so-called "no touch period") for 20 minutes for cardiac death certification by current legislation, as defined by Law n. 578 (December 29, 1993) and by the decreto del Ministro della sanità n. 582 (August 22, 1994), a unique situation in European countries. Nevertheless, because normothermic regional perfusion may ideally improve perspectives of organ viability after warm ischemia [5], DCD can be practiced even in Italy without a previous shortening of the no-touch period, which would be desirable in the near future [6].

The feasibility of the DCD in Italy has been definitively demonstrated by the initiation of a DCD program in 2005 [7] coordinated by the Centro Nazionale Trapianti (CNT), at first by Treviso, Pisa, and Cagliari Hospitals and by Pavia in 2007 (Programma Alba), mainly in the uncontrolled domain and initially for kidneys only [8]. In 2013, the combined work of the Policlinico of Monza and the Policlinico of Milan led to completion of the first DCD lung transplant. In 2015 at the Grande Ospedale Metropolitano Niguarda Hospital, the first DCD liver transplant took place; since then, the CNT produced new recommendations and guidelines [9] for organ retrieval and allocation. Since 2014, an innovative DCD protocol for lung donation has been successfully implemented using lung protective maneuvers and ex vivo reconditioning [10] with encouraging results. In 2018 in San Raffaele Hospital, Milan, the first successful pancreatic islet transplant was carried out [11]. Still, the DCD donation rate in Italy is extremely low compared with DBD, which reached, in 2018, 1714 organ donations, corresponding to 28.2 donations pmp. Big regional differences remain in the field, and DCD protocols are not extensively adopted yet, especially for controlled donation after circulatory death, which remains de facto a relatively unexploited domain throughout the country. Data published by the CNT show a positive trend in increasing DCD donations: in 2016, the total number of Italian DCD donors was 21 (14 used donors); in 2017, the DCD effective donors were 55, of which 32 used donors (0.51 pmp); and in 2018, of 73 DCD donors, most of them uncontrolled donation after circulatory death (uCDC), 47 were used (0.78 pmp) [12] (Fig 3).

Although the easiest way to implement the DCD program in Italy would be through encouraging uncontrolled DCD protocols in those hospitals that are already routinely experienced in advanced treatment of cardiovascular failure including extracorporeal life support for out-of-hospital cardiac arrest [13], cDCD has a high potential of growth that should be simultaneously investigated.

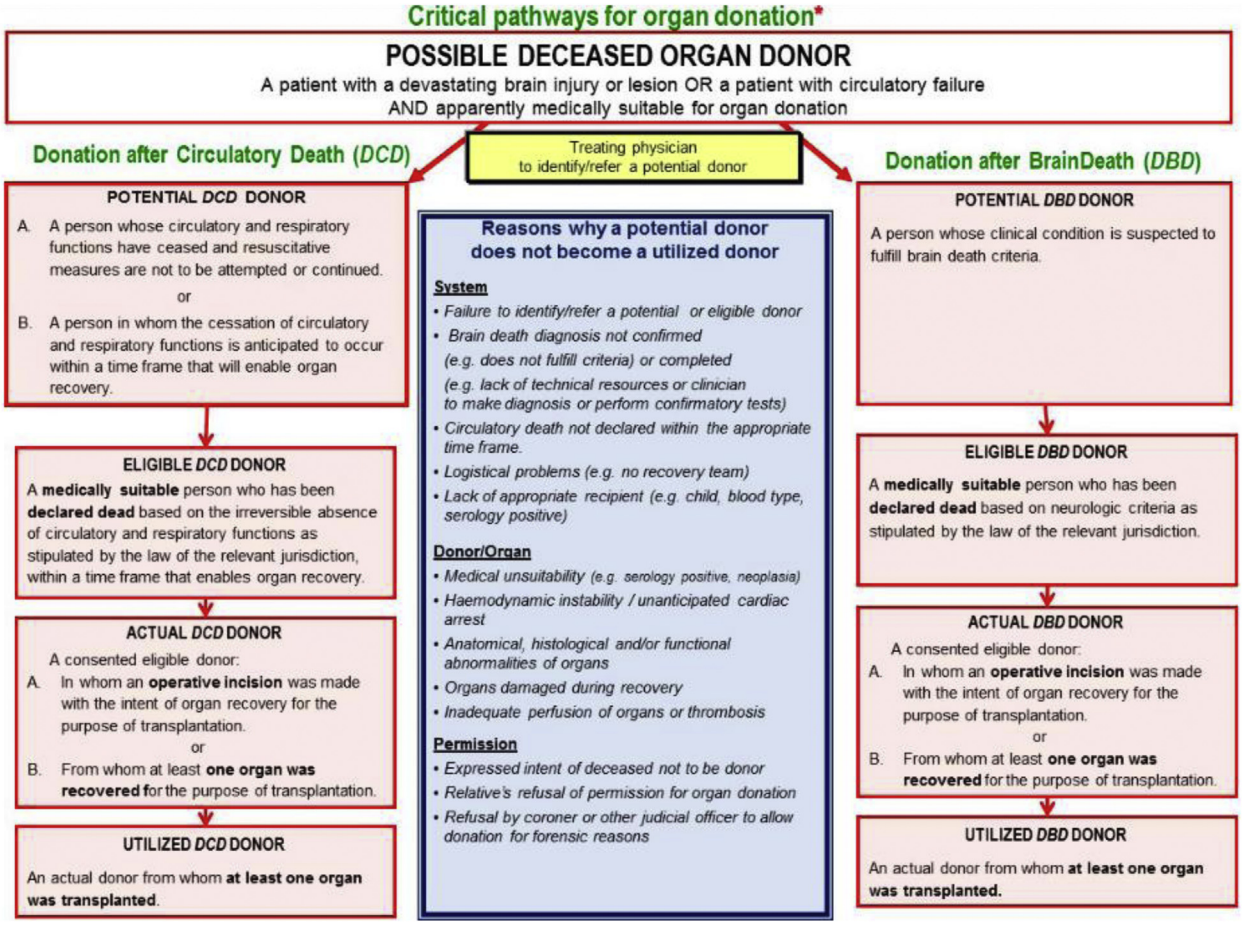

Fig 2. World Health Organization critical pathway for deceased donation [2].

Because cDCD relies on end-of-life decision and care, the extension of the adoption of WLST protocols, implemented by SIAARTI (Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva) [14,15] and a new law on end of life dispositions (2018) [16] has recently exposed the number and frequency of decisions of withdrawing life-sustaining therapies and the amount and quality of palliative care in intensive care units (ICUs), in addition to the possibility of identifying a new domain of possible organ donation.

In March 2019, the first successful liver and kidney transplantation took place in San Paolo Hospital (ASST Santi Paolo e Carlo) in Milan using controlled donation after circulatory death in a hospital without an ECMO facility.

The following analysis provides an operative tool to those hospitals with high potential in donation but without all the facilities requested to carry out controlled DCD alone.

METHODS

To estimate the dimension of the possible cDCD phenomenon in Italy, 2 different methods were applied: 1. estimation of the theoretical number of WLST in ICUs through analysis of different sources available in literature and 2. the analysis of data collected directly from the adult general 7-bed ICU of San Paolo Hospital (Milan, Italy), a governmental secondary care spoke hospital with neither neurosurgical nor major trauma facilities.

The most accurate analysis in literature on WLST procedures and end-of-life care in the Italian situation are drawn by 3 main works: the 1 carried out by the Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GiViTI) Group [17], the analysis published by Cortegiani [18], and by the End-of-Life practices in European Intensive care units: the study [19].

According to the GiViTI network, which has worked in this field since 1991 and now involves 295 out of the about 450 Italian ICUs, the data collected directly by the ICUs show a population of treated patients of approximately 150,000 people a year; approximately 20% (30,000 patients) die in the ICU, which amounts to about 82 patients every day.

A recent analysis published by Cortegiani et al states that despite the development of new technologies and the improvement of care, the death rate in ICUs remains high worldwide [20,21], ranging from 20% to 35%, which is not far from the results obtained by the GiViTI group. It seems that in recent years, ICU admissions in the last month of life have been growing up to 30% [22], which could be interpreted as part of end-of-life care. In a further study investigating factors that influence decisions to withdraw life support [23],

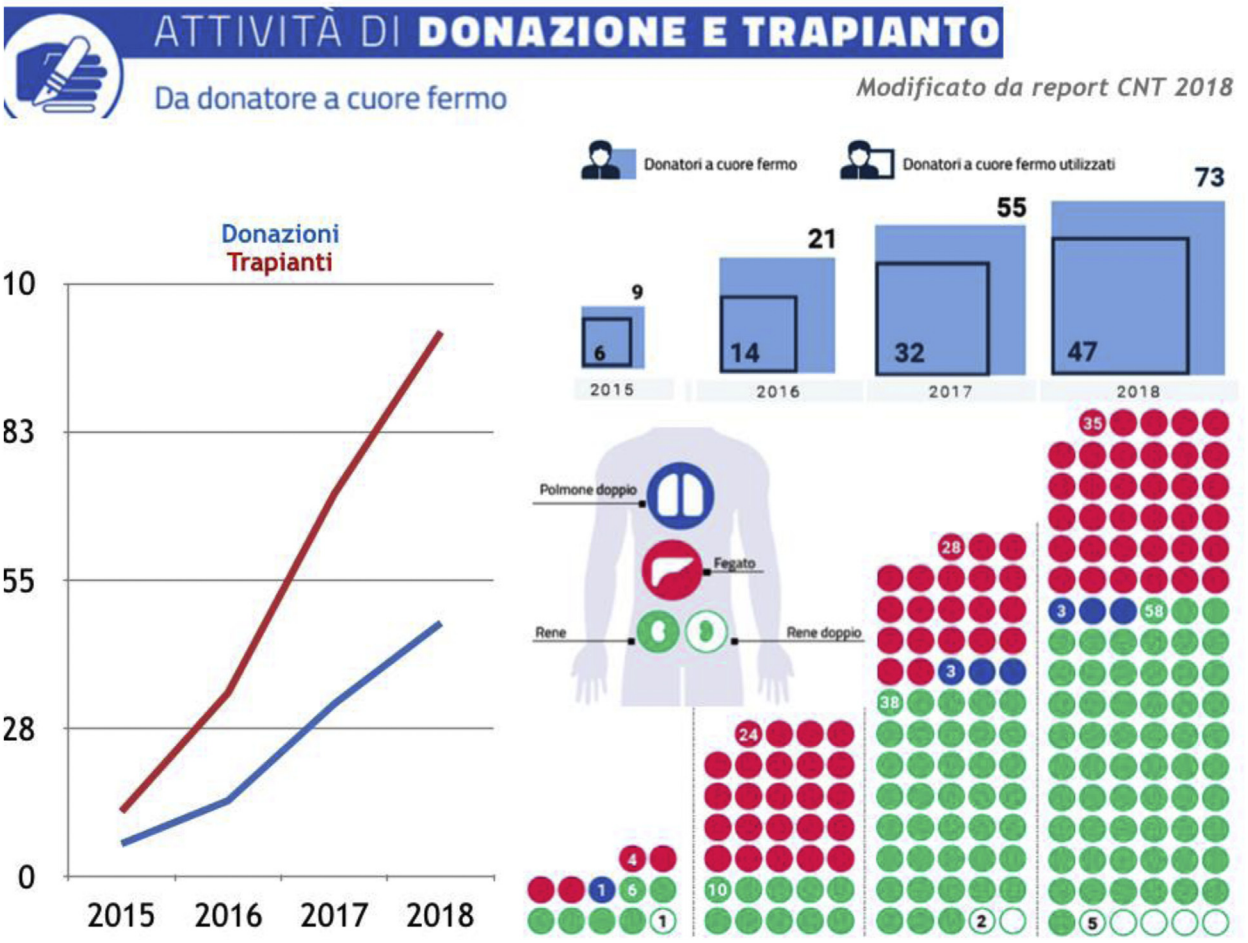

Fig 3. Donation activity report, Centro Nazionale Trapianti 2018 [12].

a total of 55% of ICU deaths were the result of treatment withdrawal, so the theoretical number of WLST in Italian ICUs is 16,500 every year. Therefore, we should look for patients who are medically suitable for donation and have expressed in life the will to donate.

Bertolini et al published in 2010 the most complete analysis available on WLST in Italy, carried out in 2005 among 38 ICUs of 3793 consecutive patients who died in the ICU or were discharged in terminal condition. Data were collected by the participating ICUs, which were adult: general (85.7%), postsurgical (7.1%), neurosurgical (4.8%), or other kind of unit (2.4%). Collection was conducted on a voluntary basis, showing that treatment limitation preceded 62% of deaths; this percentage was in line with what is described by Cortegiani. Half of the limitations were do not resuscitate orders, with the remaining half almost equally split between withholding and withdrawing treatment. The majority of patients were admitted for or developed during their ICU stay metabolic or postanoxic encephalopathy. Although the study is dated, the analysis of the demography of ICU admissions is interesting, showing a mean age of admission of 63.7 years who were mainly nonsurgical patients with respiratory failure. During the study, 31,417 patients were admitted to ICUs in 37 centers over 13.5 months. Of these 31,417, 4248 patients died or had end-of-life decisions; 3086 were patients for whom life support was withheld (52%) or withdrawn (45%) or the decision to shorten the dying process in 94 (3%) was taken by the staff. Dividing the number of these 3086 dead patients in the subset of WLST for the 13.5 months of the study, it emerges that each center should at least evaluate for cDCD in more than 6 patients per month.

A survey [24] conducted in the city of Milan by the SOREU Metropolitana (the former Emergency Operative Coordination Center) in the period of April to June 2014 in the area of Milan, its hinterland, and the Monza-Brianza Province (1.981 km^2, 4,038,864 inhabitants plus more than 1,000,000 visitors and workers every day) showed a total of 1113 out of hospital cardiac arrests, totaling 12 every day. In 783 cases, cardiopulmonary resuscitation was initiated; 234 arrived at Milanese hospitals with ongoing cardiopulmonary resuscitation. In 29 cases (12.4%), extracorporeal life support was feasible; in 30 cases (12.8%), uncontrolled DCD could be taken into account, whereas in 103 cases (44.5%), the patients were at least potential tissue donors. In total, 103 patients had a return of spontaneous circulation and were transported to the nearest hospital with coronary angiography and percutaneous coronary intervention facilities, which could be a hub or a spoke, according to distance and immediate resource availability. The survey did not include patient ICU outcomes or potential WLST decisions related

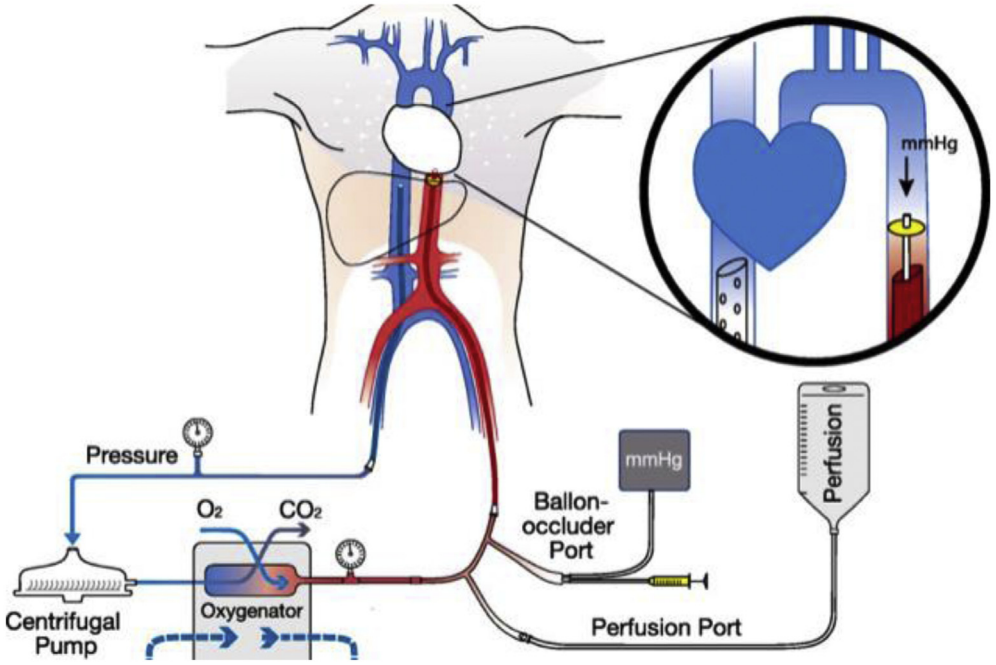

Fig 4. Extra corporeal membrane oxygenation setup for controlled donation after circulatory death [40].

to these 34 patients per month who showed no response to therapy; they were located in 17 different hospitals, totaling 2 patients per month for each center.

After analyzing the clinical charts of the last 3 years (2016 to 2018) of an average adult 7-bed ICU of Azienda Socio Sanitaria Territoriale in Milan, Italy, it appears that, in 2016, 75 patients died in the ICU, 20 of whom were younger than 65 years (34.6%). WLST was performed in 14 of these 20 patients (70% cases); 4 of them were medically suitable for organ donation.

In 2017, there were 463 patients admitted to the ICU; 70 died in the ICU, 21 were younger than 65 years, 10 (47%) had a WLST decision, and 4 were medically suitable for at least kidney and liver donation. In 2018, the total number of admissions was 442, which resulted in 47 ICU deaths; 17 of these patients were younger than 65 years, and 3 patients had no contraindication to organ donation. In conclusion, in the past 3 years, at least 3 patients per year had to be screened for controlled DCD.

Several groups have reported that normothermic regional perfusion (NRP; Fig 4) is a beneficial strategy to restore cellular metabolism and to allow evaluation of organ function, and thus organ viability, of kidneys, liver, and pancreas after cardiac death until eventual organ retrieval [25].

Hessheimer et al [26] recently published the results of the largest study published to date describing the use of postmortem NRP in cDCD liver transplantation, a propensity-matched nationwide observational cohort study, carried out between 2011 and 2016 on a total of 212 liver transplants from controlled DCD donors.

The results of this study indicate that the use of postmortem NRP can help reduce rates of post-transplant biliary complications such as postoperative biliary strictures and ischemic-type biliary lesions and improve graft survival compared with super rapid recovery, allowing successful transplantation of livers even from older cDCD donors.

The Institution of Normothermic Regional Perfusion relies on ECMO facility availability, and it is the maintenance method of choice in the Italian setting owing to longer ischemia time for death certification [27,28], as stated by CNT guidelines [29].

Theoretical Organization and Practical Aspects

The northern Italian regions have operated according to the hub-and-spoke model of hospital systems since 2002 [30]. The hub-and-spoke organization is a model that arranges service delivery assets into a network consisting of an anchor establishment (hub), which offers a full array of services, complemented by secondary establishments (spokes), which offer more limited service arrays, routing those patients needing more intensive services to the hub for treatment [31].

The hospitals have been assigned to different geographic areas; in relation to their location, a hub for each area has been identified. The spokes, that is, the network of hospitals comprised within the hub's gravitational system, are directly linked to their main hub and indirectly connected, through "hub-to-hub" connections, to spokes in other areas. This operative model was implemented during the H1N1 outbreak in 2009, when the Italian Ministry of Health identified 11 ECMO centers (now increased to 14) to which critically ill patients with H1N1-induced respiratory failure were admitted to peripheral hospitals because of the lack of centralization or spontaneous presentations and who could be transferred and centralized a second time. The 14 Italian major ECMO centers follow the International ECMO Network guidelines (ECMONet) [32] for their organization but also for the creation of the so-called mobile ECMO teams. Each ECMO network component should in fact ideally create a mobile ECMO team to retrieve patients who have critical cardiopulmonary failure refractory to conventional therapy: their coordination would run through the tertiary ECMO referral

center; should be available 24 hours a day, 7 days a week; and should employ experienced personnel trained in the transport of critically ill patients, insertion of ECMO cannulas, and circuit and patient management [33]. The team includes a mix of physicians, transport specialists, nurses, perfusionists, and other ECMO specialists.

Even in an organ donation setting, this hub and spoke model, implemented with ECMO for NRP facilities, could be feasible, especially in the event of cDCD. The fact that the controlled donation could be programmed, within some range, and that the theoretical number of cDCD, as estimated before, would be 3 to 4 per year per center, this could suggest the use of already existing ECMO teams for donation purposes. Higher distances could be covered by different hub centers. The coordination of the entire process should be under the reference of the CNT and its Inter Regional and Regional Coordination Centers, following the Spanish experience.

The mobile team organization implemented by the Complejo Hospitalario Universitario of Granada [34] has been operative since 2015, being active as a hub center for ECMO for donation purposes in different spoke hospitals. The ECMO system is managed by transplant procurement managers (TPMs) who are specialists in intensive care medicine and who work in the ICU, just as most Italian TPMs. These mobile teams are composed by a TPM, a nurse transplant coordinator, a perfusion expert, and a vascular or cardiac surgeon for ECMO cannulation; the entire team arrives at the spoke hospital with all the facilities needed to start an NRP [35].

Cost Analysis

Although the literature offers evidence that DCD is more resource intensive than DBD, because more retrievals will be required to produce the same number of organs [36] the only extensive analysis of overall costs for DCD and cost-effectiveness of DCD kidney transplantation in Italy has been carried out by the University of Pavia [37] after the beginning of the Programma Alba in 2007. To date, kidney retrieval from DCD is financed by Region Health Care System with the same reimbursement rate as kidney retrieval from DBD; the charge does not include the incremental cost related to an organ procurement program targeting DCD.

The results show that retrieving kidneys from DCD by implementing the Programma Alba protocol resulted in 2 extra transplants per year during the 2007 to 2011 period. Including recipient screening and surgery costs, patient follow-up costs, immunosuppression therapy (assuming a tacrolimus-based immunotherapy as a more cost-effective therapy), and complication costs in the year of transplant, the results indicate that changing the actual practice pattern for new patients with end-stage renal disease and increasing the availability of kidneys from DCD to 10 extra transplants per year will induce an incremental cost per quality-adjusted life-year of 4255 €, resulting in a cost-effective policy to expand the kidney donor pool, as hemodialysis costs alone are around €30,000 per year per patient (hospital hemodialysis: €37,881, home hemodialysis: €21,280, satellite hemodialysis: €31,793) and peritoneal hemodialysis around €25,000 per year per patient (continuous ambulatory peritoneal dialysis: €23,778, automated peritoneal dialysis/continuous cyclic peritoneal dialysis €27,435). Moreover, the analysis highlights that attaining 25 extra transplants from DCD per year on a national basis should produce a net saving and a net health gain in terms of hemodialysis-free days and quality of life.

Regarding the net ECMO team costs for DCD, further analysis can be performed in terms of total disposable costs and personnel costs. In fact, because the donation and retrieval would take place in the same hospital in which the donor is hospitalized, the ECMO team should only provide materials and personnel not available in the spoke hospital, and these costs must be covered by the hospital in which the identification of the donor has been performed.

In Italy, only 2 different subsets of disposable materials for ECMO treatment (circuit, pump, oxygenator) are available to date, with different cost profiles but superimposable quality, ranging from €1830 to €8418, whereas a venous cannula 23F o 21F costs €732 and an arterial cannula 21F o 19F would cost €610. To date, the medical personnel cost €30.35/h, whereas nursing staff members cost €21.97/h and nonmedical health care personnel €20.17/h [38].

RESULTS

In March 2019, San Paolo Hospital (ASST Santi Paolo e Carlo), a secondary care spoke hospital in Milan without an ECMO facility, performed the first Italian controlled donation after cardiocirculatory death of kidney and liver supported by an external ECMO team, granted by IRCCS Policlinico San Matteo, Pavia, located at a distance of 37 kilometers.

The potential donor was a 55-year-old male patient (body mass index 22.03) admitted to the ICU at San Paolo Hospital in March 2019 for severe acute respiratory distress syndrome and pulmonary embolism in recent finding of idiopathic pulmonary fibrosis. He had been on corticosteroid therapy since January 2019, with a past history of arterial hypertension, and in dual therapy since November 2018, with lower limb venous insufficiency and a previous right saphenectomy more than 10 years before. Diagnostic tests showed a cytomegalovirus infection, with CMV-DNA detected in bronchoalveolar lavage and peripheral blood, so a targeted therapy was initiated that resulted in viral load reduction after 8 days of treatment. During the ICU stay, he suffered a ventilator-associated pneumonia as a result of *Stenotrophomonas maltophilia* and progressive worsening of the respiratory failure; after 7 days of mechanical ventilation, a percutaneous tracheostomy was performed. After 15 days of therapy, without a satisfactory response and in absence of other therapeutic options, the ICU staff and the family decided on WLST. According to CNT guidelines, no contraindications to kidney and liver donation were identified, and the local procurement management interviewed the next of kin, who agreed to organ donation.

The ECMO team provided by the hub was composed by the TPM, the organ donation nurse coordinator, 1 perfusion technician, and a cardiac surgeon, who was transported along with all the material needed by an ambulance granted by the CNT. The portable facilities included were a compact mobile extracorporeal membrane oxygenation system along with 2 backup circuits; 21F and 19F arterial cannulas; 23F, 21F, and 19F venous cannulas; a portable surgery kit for cannulation; and 5, 6, 7, and 8F introducer sheaths. Before WLST was initiated by ICU staff, echo-guided percutaneous positioning of 7F introducer in the right femoral artery and right femoral vein was performed by the cardiac surgeon. No removal of the tracheostomal cannula was performed; terminal palliation was conducted following Società Italiana

di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI) recommendations on sedation and analgesia, when blood pressure drops < 50 mm Hg, heparin (300 units/kg) was administered. NRP was instituted after 55.22 minutes of functional warm ischemia time, with a mean flow of 2.4 Lpm, FiO_2 0.45, temperature 36°C to 37°C, PaO_2 100 to 130 mm Hg, and hemoglobin of 10 g/dL after 4 packed units of RBCs. Position of the supradiaphragmatic balloon was controlled radiologically with contrast medium.

After 2.5 hours of regional perfusion, performed in the ICU in the presence of the family members, the lactate started to be cleared after a peak increase was reached at the second hour of perfusion. The patient was then brought to the operating room, with a minute of silence observed by the entire staff and the family before leaving the ICU. The liver and kidney surgical teams, respectively, from IRCCS Ospedale Maggiore Policlinico (Milan) and IRCCS Policlinico San Matteo (Pavia) decided to maintain the NRP for an additional hour to let the perfusion optimize before harvesting the abdominal organs; in the meantime, a liver biopsy was performed. The visual evaluation of the surgical team and biopsy did not show any contraindication to the harvesting of the kidney and liver, which were subsequently recovered and perfused through machine perfusion till the successful transplantation of the liver and 1 kidney following CNT DCD allocation criteria. The San Paolo Hospital (ASST Santi Paolo e Carlo, Milan) has been charged by the Istituto Ricovero e Cura a Carattere Scientifico Policlinico San Matteo (Pavia) with the costs of disposable materials and the personnel costs (€5700). The Regional Health Care System has subsequently reimbursed the total amount of the kidney and liver procurement plus a fixed amount for donor identification.

The internal audit showed the need for education and training of the entire operating room staff, which must be implemented.

CONCLUSIONS

The first Italian cDCD liver and kidney donation with the help of a mobile ECMO team for NRP institution showed, in particular, the feasibility of DCD type III even in hospitals without many facilities. The hub-and-spoke model, coordinated by the CNT network, has proven to be a good model of teamwork, along with communication within the different professionals and teams and a multidisciplinary approach to the donation.

This approach to cDCD can be easily exported to other hospitals with potential organ donors who are part of the CNT network, with a mobile ECMO team provided by a spoke hospital.

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