BRIEF COMMUNICATION

Determining the impact of timing and of clinical factors during end-of-life decision-making in potential controlled donation after circulatory death donors

Angela M. Kotsopoulos[1] 🆔 | Nichon E. Jansen[2] 🆔 | Piet Vos[3] 🆔 | Marloes Witjes[1] 🆔 | Meint Volbeda[4] 🆔 | Jelle L. Epker[5] 🆔 | Hans P. C. Sonneveld[6] 🆔 | Koen S. Simons[7] 🆔 | Ewald M. Bronkhorst[8] 🆔 | Hans G. van der Hoeven[1] 🆔 | Wilson F. Abdo[1] 🆔

[1]Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

[2]The Dutch Transplant Foundation, Leiden, The Netherlands

[3]Department of Intensive Care, Elisabeth TweeSteden Hospital, Tilburg, The Netherlands

[4]Department of Intensive Care Medicine, UMCG University Medical Center, Groningen, The Netherlands

[5]Department of Intensive Care Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

[6]Department of Intensive Care Medicine, Isala Hospital, Zwolle, The Netherlands

[7]Department of Intensive Care Medicine, Jeroen Bosch Hospital, Den Bosch, The Netherlands

[8]Department of Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence
Angela M. Kotsopoulos
Email: a.kotsopoulos@etz.nl

Controlled donation after circulatory death (cDCD) occurs after a decision to withdraw life-sustaining treatment and subsequent family approach and approval for donation. We currently lack data on factors that impact the decision-making process on withdraw life-sustaining treatment and whether time from admission to family approach, influences family consent rates. Such insights could be important in improving the clinical practice of potential cDCD donors. In a prospective multicenter observational study, we evaluated the impact of timing and of the clinical factors during the end-of-life decision-making process in potential cDCD donors. Characteristics and medication use of 409 potential cDCD donors admitted to the intensive care units (ICUs) were assessed. End-of-life decision-making was made after a mean time of 97 hours after ICU admission and mostly during the day. Intracranial hemorrhage or ischemic stroke and a high APACHE IV score were associated with a short decision-making process. Preserved brainstem reflexes, high Glasgow Coma Scale scores, or cerebral infections were associated with longer time to decision-making. Our data also suggest that the organ donation request could be made shortly after the decision to stop active treatment and consent rates were not influenced by daytime or nighttime or by the duration of the ICU stay.

KEYWORDS
consent to organ donation, decision-making, donation after circulatory death, futility, withdrawal of life-sustaining treatment

1 | INTRODUCTION

The majority of deaths of patients admitted to the intensive care unit (ICU) (85%) are diagnosed based on circulatory arrest due to withdrawal of life-sustaining treatment (WLST). In these patients, 2.5% to 5% are eligible for controlled donation after circulatory death (cDCD).[1-3] Crucial steps before the initiation of a cDCD procedure are (1) prognostication, (2) actual decision to withdraw life-sustaining therapy, (3) timing of the communication of the futile prognosis with the next-of-kin, (4) family consent to organ donation, and (5) the practice of end-of-life care.[4]

Limiting life-supporting treatment is common in ICUs worldwide; however, the decision-making process and end-of-life care provided vary greatly between countries (and even between hospitals and treating physicians within a country) and are dependent on the existing local culture, religion and legislation. Attitude of the treating physician toward end-of-life care, the prognosticating ability of the physician, and patient-related factors influence the decision to limit or withdraw active medical treatment.[5-11] Timing of prognostication and initiation of end-of-life care can impact the number of potential donors.[12,13] Previous studies suggested that delaying WLST enables professional caregivers to dedicate more time to counseling relatives and providing clear information regarding the process of dying and organ donation.[14] On the other hand, Hulme et al showed that the involvements of a specialist nurse and known patient wishes were strongly associated with family approval for organ donation, whereas time from admission to family approach and time of the day were not.[15] However, the topic of timing the decision to stop active treatment and the role of clinical factors, such as medication use at the time of decision to adjust active treatment to one that focuses on end-of-life care and its impact on organ donation, is a less-studied subject.

In this context, the main aim of our study was to assess timing and patient characteristics that are associated with the decision-making process leading to the initiation of end-of-life care, in a large multicenter prospective study of potential cDCD donors. A second objective was to explore the influence of this timing in family approach on consent to organ donation.

2 | MATERIALS AND METHODS

This study is part of a multicenter, observational, prospective cohort study titled "Prediction on Time to Death in Potential Controlled Donation After Circulatory Death (cDCD) Donors (DCD III Study)" (ClinicalTrials.gov NCT04123275). In the DCD III Study, 409 consecutive potential cDCD patients admitted at the ICU of 3 university and 3 teaching hospitals in the Netherlands, were included. The main objective of the DCD III Study is to develop a model predicting time to death in potential cDCD patients. Of the cases, 80% will be used to develop the model and 20% will be used to validate the model. On different time points, data on neurologic examination, physiological variables, and dose of sedation, analgesia and vasopressors were registered and will be used to develop a prediction model. In addition, we collected data regarding end-of-life decision-making in all included patients. These data are presented here.

In a period of 40 months, all potential cDCD patients aged between 18 and 75 years who met the criteria for cDCD as defined by the Dutch Transplant Foundation were included.[16] Patients were excluded if they were younger than 18 years, were not mechanically ventilated, or were brain dead or when contraindications to organ donation were present (e.g., sepsis, malignancy, or active viral infections).

2.1 | Definition of decision-making

Decision-making was defined as the point in time that the medical team decided that further therapeutic treatment was futile.

We calculated 2 different timeframes (in hours): (1) from ICU admission until the decision of futility of treatment (decision-making) and (2) from completion of decision-making until actual WLST.

2.2 | Data collected

To assess whether timing and patient characteristics are associated with decision-making resulting in the onset of end-of-life care, we collected data at 2 different points in time. First, on admission we collected baseline patient characteristics including sex, age, APACHE IV score, and diagnosis. Second, at the point in time the medical team decided that further treatment was futile (decision-making), we assessed the Glasgow Coma Scale (GCS) score; pupillary, corneal, and cough reflexes; and type and doses of sedatives, analgesics, and vasopressors/inotropes.

Diagnosis on admission was classified according to the *International Statistical Classification of Diseases and Related Health Problems by the World Health Organization (WHO), Tenth Revision* (ICD-10) code system. Data on family consent or refusal to organ donation were collected. Data were prospectively collected by the local investigators and recorded using an electronic case report form (CRF).

If different types of opioids (e.g., morphine, sufentanil, remifentanil, or fentanyl) were used, we converted the doses in morphine equivalent doses. We estimated that 1 mg of intravenous morphine is equivalent to 15 μg of intravenous fentanyl and 2 μg of sufentanil.[17,18]

The study protocol was reviewed and approved by the ethics committee of all participating hospitals. Because the protocol included only collection of data that were components of standard care, the need for informed consent was waived. Our results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19]

2.3 | Statistical analysis

We used univariable linear regression analysis to identify factors associated with timing to decision-making. Multivariable linear

regression analysis with forward selection was performed enrolling the most significant variables based on $P < .05$, to select the strongest set of variables associated with timing to decision-making. Our database had only missing data on the APACHE IV variable (14 cases, 3.4%). The statistical analyses were performed using IBM SPSS, version 24.

3 | RESULTS

3.1 | Patient characteristics

Table 1 shows the patient characteristics of all 409 potential cDCD donors. Multivariable linear regression analysis showed that higher APACHE IV scores, intracranial hemorrhage (ICH), and ischemic cerebrovascular accident (CVA) as an ICU admission diagnosis were related to shorter decision-making time. Presence of pupillary and corneal reflexes, higher GCS score, and diagnosis on admission related to cerebral infection or neoplasm were strong predictors of longer time until decision-making (Table 2). These variables together explained 27.5% (R^2 0.275, $P = .034$) of the variance in decision-making time.

In 23 (5.6%) of cases, the decision-making toward end-of-life care was finalized before ICU admission. Table S1 outlines the clinical characteristics of these patients. The majority of these patients had devastating traumatic brain injury (TBI) or ICH, lacked pupillary and corneal reflex reactions, and were treated with high doses of morphine equivalents and/or propofol.

3.2 | Medication on decision-making

In 32% of the patients, vasopressors were administered, mostly norepinephrine. Propofol (19%) was the most used sedative, followed by midazolam (13%). The majority of patients (71%) had no sedation or opioids (65%) on decision-making. Mean doses of vasopressors, sedatives, and opioids are shown in Table 1.

Patients with a TBI, SAH, or ICH received significantly lower doses of analgesia on decision-making compared with postanoxic patients (Table S2).

3.3 | Timeframes from ICU admission until WLST

3.3.1 | Admission to decision-making

Mean and median time from admission until decision-making for the total cohort of 409 patients were 97 ± 127 hours (SD) and 48 hours (IQR 15 to 134 hours), respectively. The mean and median times until decision-making, excluding the 23 patients in whom end-of-life decision was made before ICU admission, were 103 ± 128 hours (SD) and 55 hours (IQR 19 to 138 hours), respectively. In these 23 patients, the decision to admit them to the ICU was to give the family more

time to grieve, to wait for the arrival of family members, or to facilitate organ donation.

3.3.2 | Day vs night

More than half of the patients (54.3%) were admitted in the evening or at night. Decision-making was mainly done during the daytime (n = 328 [80%]). When the decision was made during a day shift, clinicians needed significantly more time compared with evening and night time (107 vs 57 hours, $P = .002$).

The shortest time between ICU admission and decision-making to stop active treatment was in those patients in whom both the ICU admission and decision of futility of treatment were made during the night (mean 3 hours). In this subgroup, significantly more patients had devastating intracranial hemorrhage with severe neurological symptoms, leaving physicians with no treatment options.

3.3.3 | Decision-making to WLST

Time from decision-making to the actual moment of WLST was significantly longer in those patients who donated their organs (mean ± SD, 14 ± 13.9 hours) compared with those patients for whom the family refused organ donation (mean ± SD, 8.9 ± 11.9 hours, $P ≤ .001$), reflecting the additional time needed to coordinate an organ procurement procedure.

3.4 | Family consent to organ donation

Organ donation was requested in all cases; however, only 127 (31%) families consented to organ donation. All families were approached for organ donation after futility of further treatment was established and options were discussed with the family. Neither the time from ICU admission to family approach for organ donation consent nor the timing of the organ donation request (during daytime or evening/nighttime) was associated with higher family consent rates to organ donation. Consent rates (39%) were also comparable when the decision-making was made before ICU admission (Table S1).

4 | DISCUSSION

This is the largest prospective multicenter observational study on the end-of-life decision-making process in potential organ donors. Previous studies using mortality prediction models for ICU patients cannot be generalized to the organ donation field because they incorporated variables that exclude the possibility of organ donation (e.g., cancer, sepsis).[5-7] In our cohort of 409 potential cDCD donors, we found that severity of disease (APACHE IV score) and extensive neurological involvement (as seen in ICH) on admission were the strongest patient-related characteristics contributing to a shorter

TABLE 1 Demographic and clinical data of 409 potential cDCD patients on decision-making

Parameters	n (%)	Mean (SD)	B	95% CI		P
Decision-making time, h		97 (127)				
Age, y		57.6 (13.6)	0.096	−0.812	1.005	.835
Male, n (%)	249 (61)		2.87	−22.4	28.2	.824
APACHE IV		93 (25.8)	−0.753	−1.237	−0.268	.002
Anoxic, n (%)[a]	103 (25)		98.3	74.3	122	
TBI, n (%)	94 (23)		6.05	−28.6	40.7	.732
SAH, n (%)	84 (21)		3.09	−32.6	38.8	.865
ICH, n (%)	72 (18)		−40.9	−78.2	−3.56	.032
CVA, n (%)	33 (8)		−27.5	−76.2	21.0	.265
Respiratory, n (%)	10 (3)		93.9	13.4	174	.022
Other, n (%)[b]	13 (3)		125	53.7	196	.001
GCS score		3.97 (1.71)	27.4	20.6	34.1	<.001
Pupillary reflex present, n (%)	193 (47)		91.4	68.2	114	<.001
Corneal reflex present, n (%)	200 (49)		85.3	60.0	110	<.001
Cough reflex present, n (%)	239 (58)		68.8	37.2	96.4	<.001
Norepinephrine dose, µg/kg/min		0.188 (0.25)				
Vasopressor use, n (%)[a]	132 (32)		−35.3	−61.5	−9.12	.008
Morphine equivalent doses, mg/h		11.38 (15.8)				
Analgesia use, n (%)[a]	143 (35)		−6.39	−32.3	19.5	.628
Midazolam use, n (%)[a]	53 (13)		−11.3	−48.1	25.4	.546
Midazolam dose, mg/h		14.9 (13.4)				
Propofol use, n (%)[a]	77 (19)		−54.4	−85.6	−23.3	.001
Propofol dose, mg/h		206 (135)				
Sedation use, n (%)[a]	120 (29)		−34.8	−58.1	−11.5	.003
Mechanical ventilation before/on admission, n (%)	329 (80)					
Family consent, n (%)[a]	127 (31)		14.0	−12.3	40.5	.296
Daytime admission, n (%)[a]	187 (45)					
Daytime decision-making, n (%)[a]	328 (80)		49.0	18.4	79.7	.002

TABLE 1 (Continued)

Parameters	n (%)	Mean (SD)	B	95% CI		P
Hemicraniectomy, n (%)[a]	48 (12)		20.4	−17.8	58.8	.295

Note: Baseline patient characteristics of 409 potential cDCD patients on admission and on decision-making. Univariable linear regression analysis on decision-making time with *P*-values. *B* is the unstandardized coefficient.

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; CI, confidence interval; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale score; ICH, intracranial hemorrhage; Resp, respiratory disease; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Parameters: APACHE IV (continuous variable), anoxic,[a] TBI, SAH, ICH, SAH, respiratory, other, GCS (continuous variable), pupillary reflex (absent, present,[a] not assessable [data not shown]), corneal reflex (absent, present,[a] not assessable [data not shown]), cough reflex (absent, present,[a] not assessable [data not shown]), vasopressor use (yes[a] or no), analgesia use (yes[a] or no), midazolam use (yes[a] or no), propofol use (yes[a] or no), family consent to organ donation (yes[a] or no), daytime admission (day[a] or evening/night), daytime decision futile treatment (day[a] or evening/night), hemicraniectomy (yes[a] or no).
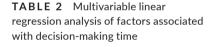
[a]Is reference.

[b]Other includes encephalitis, Huntington disease and trauma, meningitis, intracerebral abscess, aspiration pneumonia complicating minor trauma, complication after meningioma resection, methanol intoxication, and refractory epilepsy.

timeframe until prognostication of futility of treatment. Additionally, we showed that in potential cDCD donors, clinicians required on average 4 days to establish a prognosis of futility. The majority of patients had sedation and/or analgesia discontinued at the moment of decision-making in order not to interfere with neurological examination and prognostication. Family refusal rates to organ donation was not associated with the timing of the organ donation request (neither the time between admission until organ donation request nor the moment of requesting being in daytime or nighttime hours).

There is a debate regarding the time needed for prognostication purposes and onset of end-of-life care. In 2015, the Neurocritical Care Society recommended delaying any decision on end-of-life treatment within 72 hours after admission in patients with devastating brain injury in order to not miss any potential good outcome.[20]

TABLE 2 Multivariable linear regression analysis of factors associated with decision-making time

	Unstandardized coefficients			95% CI		
	B	SE	t			P
(Constant)	76.25		2.833	23.32	129.1	.005
APACHE IV	−0.87	−0.175	−3.912	−1.32	−0.43	<.001
ICH	−41.96	−0.126	−2.777	−71.67	−12.25	.006
CVA	−44.00	−0.096	-2.129	−84.67	−3.36	.034
Other[a]	79.84	0.108	2.244	15.03	144.60	.016
Pupillary reflex present	50.35	0.196	3.927	25.13	75.56	<.001
Corneal reflex present	35.37	0.138	2.837	10.86	59.89	.005
GCS	17.55	0.237	5.056	10.72	24.38	<.001

Note: Multivariable linear regression analysis with forward selection of patient characteristics associated with decision-making time. Analysis included 409 potential cDCD patients. Multivariable linear regression analysis with forward selection. Adjusted for age, sex, diagnosis (categorized as postanoxic,[a] TBI, SAH, ICH, SAH, respiratory, other), GCS (continuous), pupillary reflex (absent, present,[a] not assessable), corneal reflex (absent, present,[a] not assessable), cough reflex (absent, present,[a] not assessable), use of vasopressor (binary), use of sedation (binary), use of analgesia (binary), APACHE IV, admission time of the day (binary; day or evening/night), decision time of the day (binary; day or evening/night).

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; CI, confidence interval; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; SE, standard error; TBI, traumatic brain injury.[a]Is reference.

[b]Other includes: encephalitis, Huntington disease and minor trauma, meningitis, intracerebral abscess, aspiration pneumonia complicating minor trauma, complication after meningioma resection, methanol intoxication, refractory epilepsy.

In addition, The European Resuscitation Council and the European Society of Intensive Care Medicine recommend to wait ≥ 72 hours after return of spontaneous circulation in post–cardiac arrest patients, before predicting poor outcome. They also mention that some indicators can be evaluated earlier, allowing earlier WLST.[21] The mean decision-making time was 97 hours in our cohort. If we exclude those patients that were admitted to the ICU with a prognosis of futility of treatment already made in the emergency department, in 57% of our cases decision-making was made after 48 hours of admission. Admission to the ICU and delaying WLST not only are considered to be beneficial for grieving families but have a positive influence on post mortal organ donation consent and number of organs retrieved.[12,22,23] Also, some patients will clinically progress to develop brain death during the observation period, allowing a donation after brain death (DBD) rather than a cDCD procedure.[14,24] A previous study showed that end-of-life decision-making was predominantly based on neurological reasons rather than ethical considerations or severe comorbidity.[25] In our cohort, decision-making was realized in a shorter period of time in a considerable number of patients. These patients had many clinical risk factors of poor outcome, which may have led to early decision-making. Stopping further treatment is a complex process where different factors influence such a decision. Deteriorating clinical status can render further treatment futile. However, treatment can also be withdrawn based on poor expected functional outcomes or on advance patient directives not in line with treatment, factors that are often known before a period of 72 hours.

Previously, age, diagnosis, acute admission of previous healthy patients, and functional status were characteristics found to be related to a decision to initiate end-of-life care.[6,7,10,12,26-28] Potential cDCD donors are a unique category of patients in terms of physiological stability. Decision-making is not based on hemodynamic, respiratory, or renal failure in these patients. As such, organ failure would render them unsuitable as potential organ donors. Thus, apart from the neurological injury, most potential organ donors have good functionality of their organs. Therefore, neurological determinants, also assessed in this study, play a central role in the prognostication of organ donors.

Administration of sedation and/or analgesia can influence (prolong) the time needed for clinical evaluation. Previous studies did not assess the dosing of sedation or analgesia and their influence on time to decision of treatment futility. We found that sedatives or opiates were not administered in 2 of 3 patients at the moment of prognostication. Prognostication in these patients with SAH, TBI, or ICH mandate that factors influencing bedside neurological judgment should be removed as much as possible. As such, analgesia and sedation were likely discontinued in these patients in order to not confound the clinical neurological examination needed for prognostication. In postanoxic patients, analgesia and/or sedation does not interfere with additional neurophysiological testing such as a somatosensory evoked potential, used for prognostication purposes. This may have explained the lower dosages of analgesia in patients with TBI, SAH, or ICH compared with the dosages used in postanoxic patients.

A crucial part in organ donation is family consent rates. If the extent of the brain injury is not communicated well or the family did not have sufficient time to understand and accept its consequences, this will result in lower consent rates to organ donation.[22] In this study, the time between ICU admission and the decision of futility of treatment was not associated with family consent rates to organ donation. Nor did the daytime or nighttime timing of the organ donation request influence consent rates to organ donation, which corroborates a previously published study.[15] We expected that shorter time intervals from ICU admission to decision-making and organ donation request would have a negative influence on family consent rates. A possible explanation is that the overall mean time between ICU admission and prognosis of futility was already long enough at 97 hours, a timeframe that is probably sufficient to have several conversations, gain trust with the family, and allow them to understand the nature of the disease and the organ donation process.

Although this is one of the largest prospective multicenter cohort of consecutive potential cDCD donors, there are some limitations to our study. We described the patient characteristics and other patient-related factors collected from admission at the ICU until the decision of futility of treatment and WLST. We did not interview the medical team members and, thus, had no insight as to which factors were precisely used to decide on futility of treatment. Other factors such as known patient wishes, specific family wishes, or premorbid physical state could have influenced the decision to withdraw treatment and its timing. There are large differences in organ donation and end-of-life practices worldwide influenced by culture and religion specific customs, resources, practices, and regulations. Although we performed a multicenter study, all study sites were located in the Netherlands. Our data could therefore be less generalizable to other countries.

In summary, our data from a large prospective cohort of 409 potential cDCD donors provide valuable insights on the largely overlooked topic of end-of-life decision-making in potential organ donors and show that early prognostication occurs in certain patient categories more often. Our data also shed light on the WLST process in potential DCD donors. Additional research is needed to explore the influence of region specific customs (religion, regulations, practices, etc.).

In addition, as a family needs time to accept the impeding (acute) death of their loved ones, early decision-making and early organ donation requesting could be seen as counterproductive. Our data show that this is not necessarily the case. Although prognostication is more difficult in the acute setting, our data show that if the treating team believes decision-making about WLST is possible early after hospital admission, this will not necessarily have a negative effect on the consent rates to organ donation. It is important to note that in all our cases, organ donation requesting was done primarily by (ICU) teams trained in organ donation requesting as is normal practice in the Netherlands. Also, most decision-making was done on a multidisciplinary basis and included key neurological clinical parameters but also took into account patient advance directives.

DISCLOSURE

AUTHOR CONTRIBUTIONS

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Angela M. Kotsopoulos https://orcid.org/0000-0003-4380-6744

Nichon E. Jansen https://orcid.org/0000-0003-2952-3799

Piet Vos https://orcid.org/0000-0003-2701-5459

Marloes Witjes https://orcid.org/0000-0002-8868-5141

Meint Volbeda https://orcid.org/0000-0001-7641-1330

Jelle L. Epker https://orcid.org/0000-0002-2256-4152

Hans P. C. Sonneveld https://orcid.org/0000-0002-8013-6228

Koen S. Simons https://orcid.org/0000-0001-8120-5566

Ewald M. Bronkhorst https://orcid.org/0000-0003-0953-8053

Hans G. van der Hoeven https://orcid.org/0000-0001-5362-0244

Wilson F. Abdo https://orcid.org/0000-0002-5783-8643

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.