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Clinical paper

Capnometry predicts the viability of procured kidneys from uncontrolled donation after circulatory death donors

Carlos Rubio-Chacón [a,*], *Alonso Mateos-Rodríguez* [b,c], *Fernando Neria* [c], *Juan Ignacio Torres-González* [d], *Mario Fernández-Ruiz* [e,f,g], *Amado Andrés* [g,h]

Abstract

Introduction: Although uncontrolled donation after circulatory death (uDCD) donors provide kidney transplants with excellent long-term survival rates, a significant percentage of grafts are eventually found not to be viable for transplantation. Capnometry during cardiopulmonary resuscitation (CPR) is a marker of tissue metabolism and organ perfusion. We analyzed whether capnometry values in potential uDCD donors could help to differentiate between valid (who provided at least one transplantable kidney) and futile uDCD donors (those not yielding suitable grafts for transplantation).

Material and methods: This study was performed at two transplant centers between January 2018 and December 2023. Patients who had unsuccessful out-of-hospital CPR attempt after cardiopulmonary arrest (CPA) and met the criteria for uDCD were selected. Capnometry values were analyzed at the start of CPR, at the midpoint and at arrival at the hospital (transfer), along with other prehospital variables that could influence the selection of a viable donor.

Results: Overall, 69 potential uDCD donors were included, of which 26 (37.7 %) were valid and 43 (62.3 %) were futile. The capnometry values in valid donors compared to futile donors were 24.5 mmHg versus 16 mmHg at the initial reading (*P*-value <0.078) and 26 mmHg versus 15 mmHg at transfer, respectively (*P*-value <0.004). The optimal cut-off value for transfer capnometry levels to discriminate viable from futile donors was 17 mmHg. In the multivariable model, mechanical chest compression (odds ratio [OR]: 14.29; *P*-value = 0.009), transient return of pulse (OR: 19.0; *P*-value = 0.013), donor age (OR [per one-year increase]: 0.91; *P*-value = 0.026) and capnometry values at arrival at hospital (OR [per one-mmHg increase]: 1.08, *P*-value = 0.012) were independent predictors of donor viability.

Conclusions: Capnometry obtained at hospital arrival is useful for identifying valid uDCD donors. In addition, younger donor age, use of mechanical chest compression devices, and transient return of pulse are prehospital variables that also increase the odds of viability in this type of donors.

Keywords: Capnometry, Uncontrolled donation after circulatory death donors, Emergency, Transient return of pulse, Transient pulse recovery

Introduction

Uncontrolled donation after circulatory death (uDCD) requires costly and complicated logistics that involve many healthcare resources, both human and material, over a short period of time.[1–3] Overall, this donation procedure yields kidneys that, once transplanted, have excellent short- and long-term survival rates.[4,5] However, many uCDC donors are futile because, following macroscopic examination, both of the procured kidney grafts are considered unsuitable for transplantation. In fact, more than 35 % of kidneys generated by uDCD programs are rejected for transplantation,[3] leading to frustration among the healthcare teams involved in these procedures and incurring in unnecessary economic costs. Keeping kidneys viable and free of irreversible ischemic damage for an average of 120 min through chest compressions and mechanical ventilation is the major challenge in this type of donation.[1–3] The kidneys of uDCD donors are subjected to significant ischemic stress, which in many

* Corresponding author at: Emergency Medical Service of the Community of Madrid (SUMMA 112), Calle Antracita 2 bis, 28405 Madrid, Spain.
E-mail address: carruch@msn.com (C. Rubio-Chacón).

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cases results in the non-viability for transplantation and delayed graft function in those that are ultimately transplanted.[3] Donor age, warm ischemia times, and type of cardiac compression (manual or mechanical) have been associated with the results of kidney grafts from these donors and, to a lesser extent, with the futility of the procedure.[6,7]

Capnography is a non-invasive and continuous measurement of the partial pressure of carbon dioxide (pCO_2) in exhaled lung air as a function of time during each respiratory cycle. This method provides an indirect assessment of ventilatory function, cardiac output, and cellular metabolism.[8,9] Capnometry during cardiopulmonary resuscitation (CPR) after cardiopulmonary arrest (CPA) is indicative of organ perfusion and cellular metabolism. Therefore, it is used as a tool to assess CPR quality and predict spontaneous circulation recovery.[10]

In the context of out-of-hospital CPA, capnometry is a useful tool for monitoring the effectiveness and quality of chest compressions, with prognostic relevance. It is known that end-tidal pCO_2 ($EtCO_2$) values below 10 mmHg during CPR, maintained over time, are associated to insufficient cardiac output and very poor survival rates.[11,12] An increase of up to three times the baseline value predicts the return of spontaneous pulse.[13,14]

In the setting of uDCD, capnometry values, as an indirect measure of tissue perfusion, could identify viable donors (those who yield kidney grafts suitable for transplantation) and rule out futile donors whose kidneys are eventually discarded. In previous studies, we have described the role of capnometry in the short- and medium-term evolution of kidney transplants from uDCD donors.[15,16]

The aim of the present study was to analyze whether capnometry values are predictive of the viability of potential uDCD donors.

Patients and methods

Study setting and design

We performed an observational, ambispective study that was conducted in the Community of Madrid (Spain) between January 2018 and December 2023, and involved two tertiary care centers with long-established transplant programs (Hospital Universitario “12 de Octubre” [HU12O] and Hospital Clínico Universitario San Carlos [HCUSC]) and the out-of-hospital Emergency Medical Service (EMS) of the Community of Madrid (SUMMA 112). The study was approved by the Research Ethics Committee of the Universidad Francisco de Vitoria (number 33/2018). The research was performed in accordance with the ethical standards outlined in the Declarations of Helsinki and Istanbul.

Patients who suffered out-of-hospital CPA, did not respond to advanced CPR attempts, and met the inclusion criteria described in the operational protocol in place prior to March 2020 —and the subsequently updated protocol from June 2021— were potentially eligible as uDCD donors.

The inclusion criteria prior to March 2020 were as follows: patients who suffered a witnessed CPA; aged 16 to 60 years; time of arrival of the advanced life support (ALS) team <15 min; time of advanced CPR $\leq$20 min; 12-lead electrocardiogram (ECG) tracing showing asystole; time interval between the onset of CPA to the arrival at the hospital <120 min. The inclusion criteria established in the updated protocol (June 2021) were essentially coincident, except that age limits were set between 18 and 50 years, and the requirement for a negative test for coronavirus disease 2019 (COVID-19).

The exclusion criteria in both protocols included thoracic and/or intraabdominal bleeding trauma; presence of neoplastic or infectious disease; intravenous drug use; and a chest circumference not compatible with mechanical chest compression.

A number of variables were prospectively recorded for each potential uDCD donor: age, gender, body mass index, past medical history, cause and location of CPA, reason for calling for assistance from the EMS, basic or advanced life support procedures at the onset of CPA, time from CPA to the arrival at the hospital, type of chest compression (mechanical or manual), transient return of pulse and capnometry values. Capnometry values were recorded at three time points. Initial capnometry was the first value recorded by the EMS after initiating treatment for the CPA, once the patient was intubated. Midpoint capnometry was the level recorded at the time halfway between the initial reading and the measurement taken upon arrival at the hospital. Transfer capnometry was the last measurement recorded by the EMS at arrival at the hospital, immediately before the patient was transferred to the intensive care unit. The capnometry trend is defined as the differences between transfer and initial capnometry readings. The occurrence of primary non-function and one-year graft and patient survival were recorded for effective KT recipients.

An uDCD donor was considered to be valid if it yielded a kidney graft that was ultimately transplanted. Conversely, the uDCD donor was defined as futile if both kidneys were discarded as being unsuitable for transplantation. The acceptance rate for non-renal abdominal organs (such as the liver and pancreas) is very low, and discard is the rule if the kidneys are unsuitable for transplantation.

Data on the donors and recipients were retrieved from electronic medical records accessed through the HORUS system, a software platform that shares clinical information from all the patients attended by the Public Health Service of the Community of Madrid. Information that was not available at the HORUS platform was completed by consulting the paper-based and electronic records of the participating centers and the Spanish National Transplant Organization (Organización Nacional de Trasplantes [ONT]).

Statistical analysis

Quantitative variables were expressed as the median with interquartile range (IQR) and qualitative variables as absolute and relative frequencies (n [%]). Categorical variables were compared using the χ^2 test or Fisher’s exact test, as appropriate. The associations between qualitative and quantitative variables (i.e. capnometry levels) were assessed using the Wilcoxon test.

We performed a multivariable analysis by logistic regression to identify independent predictors of valid uDCD donor. The model included those variables with a *P*-value <0.2 in the univariable model, as well as capnometry levels as the independent variable of interest. Model fit was assessed using McFadden’s Pseudo R^2 and model calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test. The results of the adjusted model were as odds ratios (OR) with 95 % confidence intervals (CIs).

The capacity to discriminate between valid and futile uDCD donors was assessed by separate areas under receiver operating characteristic curve (auROCs) generated for each variable and for the multivariable model, whereas the optimal cut-off values were investigated by the Youden’s J index (J = sensitivity + specificity − 1). In addition, the diagnostic performance was evaluated by the sensitivity, specificity, positive (PPV) and negative predictive values (NPV). All the statistical analysis was performed using R software v 4.1.

Results

Between January 2018 and December 2023, a total of 69 potential uDCD donors were identified and transported by the EMS to the participant centers. These patients underwent kidney extraction for transplantation (40 [57.9 %] at the HCUSC and 29 [42.1 %] at the HU12O). Out of these 69 potential uDCD donors, 26 (37.7 %) were valid and 43 (62.3 %) were futile (Fig. 1). Data completeness was high, with a mean missingness rate of 4.3 % across all variables. The characteristics of the CPA are detailed in Table 1. There were no differences between valid and futile uDCD donors according to the reason for calling, location of CPA, initial ECG rhythm or life support procedures before the arrival of EMS.

The median capnometry levels of the entire cohort of potential uDCD donors were 19.0 [IQR: 12.0–32.0] mmHg at the onset of CPA (initial capnometry), 23.0 [IQR: 16.0–34.0] mmHg at the midpoint of CPA, and 22.0 [IQR: 12.5–30.5] mmHg upon arrival at the hospital (transfer capnometry). When only the subgroup of 26 valid donors was considered, the corresponding values were 24.5 [IQR: 13.0–35.0] mmHg, 22.5 [IQR: 18.0–36.0] mmHg and 26.0 [IQR: 20.0 –32.0] mmHg, respectively. The 43 donors that eventually resulted to be futile had a median capnometry values of 16.0 [IQR: 10.0–29.0] mmHg at the onset of CPA, 23.5 [IQR: 16.0–32.0] mmHg at the midpoint, and 15.0 [10.0–29.0] mmHg at hospital transfer (Table 2).

We next compared the capnometry measurements in both groups. The median values in valid and futile donors at the onset of CPA (initial capnometry) were 24.5 (IQR: 13.0–35.0) and 16.0 (IQR: 10.0–29.0) mmHg, respectively (*P*-value = 0.078). This difference was statistically significant for the values obtained at hospital arrival (transfer capnometry), with 26.0 (IQR: 20.0–32.0) mmHg in valid donors as compared to 15.0 (IQR: 10.0–29.0) mmHg in futile donors (*P*-value = 0.004).

In the multivariable model, the prehospital factors that were shown to act as independent predictors of uDCD donor viability were donor age (OR [per one-year increment]: 0.91, 95 % CI: 0.83–0.98; *P*-value = 0.026), mechanical chest compression (OR: 14.28; 95 % CI: 2.38–100; *P*-value = 0.009), transient return of pulse at some point during CPR (OR: 19.0; 95 % CI: 2.24–265; *P*-value = 0.013), and transfer capnometry at arrival at the hospital (OR [per one-mmHg increment]: 1.08; 95 % CI: 1.02–1.16; *P*-value = 0.012). Donor gender, time interval from the initiation of advanced CPR techniques to hospital arrival and death from cardiac causes, on the other hand, were not significantly associated with valid uDCD donor (Table 3).

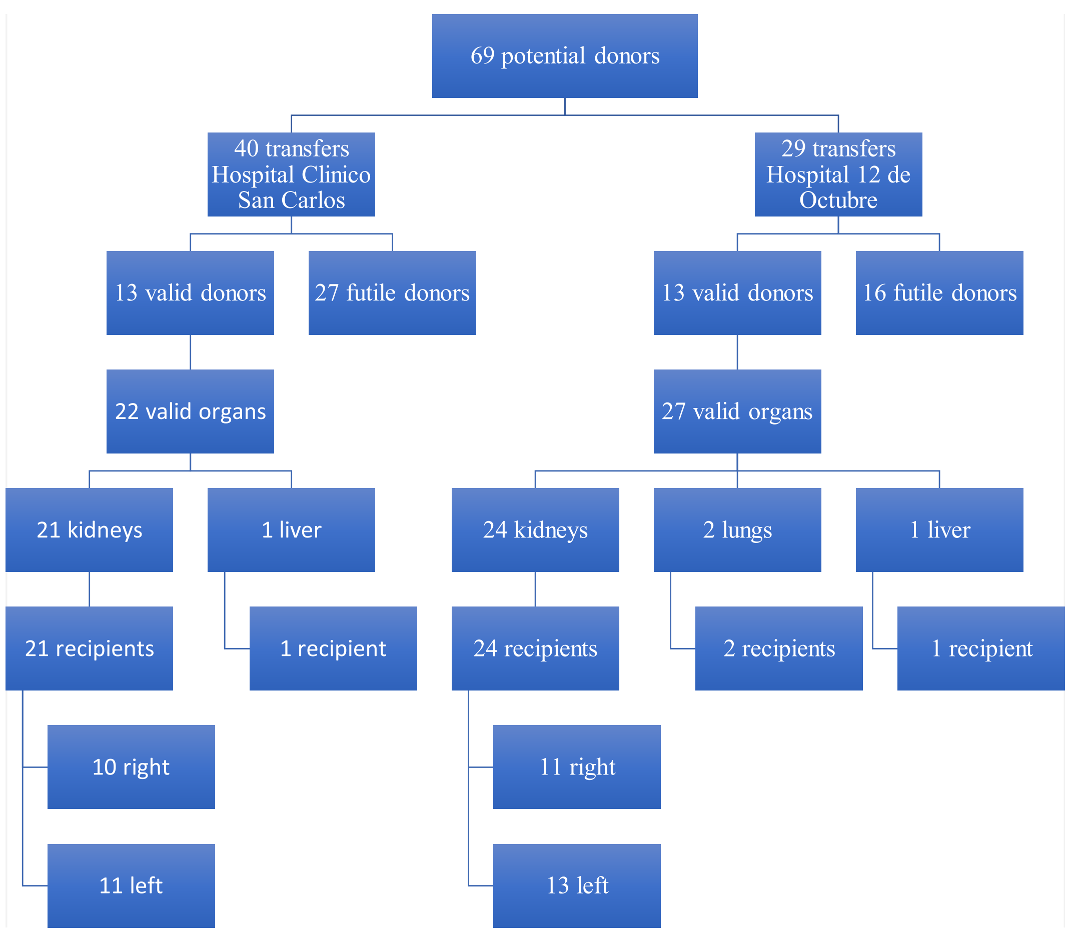

Fig. 1 – Flow chart of uncontrolled donation after circulatory death (uDCD) donors at the two participant centers during the study period.

Table 1 – Comparison of characteristics of the CPA between valid and futile uDCD donors.

	Overall cohort N = 69	Futile uDCD donor N = 43	Valid uDCD donor N = 26	*P*-value
Reason for calling for emergency assistance [n (%)][a]				0.551
Cardiac arrest	35 (58.3)	19 (54.3)	16 (64.0)	
Unconsciousness or coma	12 (20.0)	8 (22.9)	4 (16.0)	
Seizures	6 (10.0)	2 (5.7)	4 (16.0)	
Syncope	4 (6.7)	3 (8.6)	1 (4.0)	
Chest pain	1 (1.7)	1 (2.9)	0 (0.0)	
Dyspnea	2 (3.3)	2 (5.7)	0 (0.0)	
Location of CPA [n (%)]				0.537
Home	43 (62.3)	23 (53.5)	20 (76.9)	
Street	14 (20.3)	10 (23.3)	4 (15.4)	
Workplace	4 (5.8)	3 (7.0)	1 (3.9)	
Recreational facility	3 (4.3)	3 (7.0)	0 (0.0)	
Public building	2 (2.9)	2 (4.7)	0 (0.0)	
Non-hospital healthcare facility	2 (2.9)	1 (2.3)	1 (3.9)	
Not specified	1 (1.4)	1 (2.3)	0 (0.0)	
Initial ECG rhythm [n (%)]				0.324
Ventricular fibrillation	27 (39.1)	14 (32.6)	13 (50.0)	
Asystole	21 (30.4)	16 (37.2)	5 (19.2)	
Pulseless electrical activity	17 (24.6)	11 (25.6)	6 (23.1)	
Pulseless ventricular tachycardia	4 (5.8)	2 (4.7)	2 (7.7)	
Life support procedures before the arrival of EMS [n (%)]				0.803
Basic	50 (72.4)	30 (69.8)	20 (76.9)	
Advanced from the onset of CPA	14 (20.3)	9 (20.9)	5 (19.2)	
None	5 (7.2)	4 (9.3)	1 (3.8)	
Procedure performed by [n (%)]				0.399
Bystander with no medical education	15 (28.3)	9 (28.1)	6 (28.6)	
Police officer or firefighter	12 (22.6)	7 (21.9)	5 (23.8)	
Patient's partner	11 (20.8)	6 (18.8)	5 (23.8)	
Emergency medical technician	5 (9.4)	4 (12.5)	1 (4.8)	
Bystander with medical education	4 (7.5)	1 (3.1)	3 (14.3)	
Primary care unit	2 (3.8)	1 (3.1)	1 (4.8)	
Other	4 (7.5)	4 (12.5)	0 (0.0)	

CPA: cardiopulmonary arrest; ECG: electrocardiogram; EMS: Emergency Medical Service; uDCD: uncontrolled donation after circulatory death.

[a] Data not available for 9 patients.

[b] Data not available for 11 patients.

Table 2 – Comparison of capnometry values at different points between valid and futile uDCD donors.

Capnometry values, mmHg [median (IQR)]	Overall cohort N = 69	Futile uDCD donor N = 43	Valid uDCD donor N = 26	*P*-value
At the onset of CPR	19.0 [12.0–32.0]	16.0 [10.0–29.0]	24.5 [13.0–35.0]	0.078
At the midpoint	23.0 [16.0–34.0]	23.5 [16.0–32.0]	22.5 [18.0–36.0]	0.259
Transfer capnometry	22.0 [12.5–30.5]	15.0 [10.0 –29.0]	26.0 [20.0–32.0]	0.004
Capnometry trend	0.0 [−9.0–9.0]	−1.0 [−6.0–6.0]	1.5 [−10.0–9.0]	0.861

CPR: cardiopulmonary resuscitation; EMS: Emergency Medical Service; IQR: interquartile range; uDCD: uncontrolled donation after circulatory death.

The optimally selected cut-off value for capnometry at time of transfer by the EMS was 17 mmHg, with this parameter showing the best diagnostic accuracy to correctly classify a given uDCD donor as valid or futile. This cut-off point predicts 24 out of the 26 (92.3 %) of the valid donors. In the case of futile donors, 23 out of 43 (60.5 %) were accurately classified. This diagnostic performance resulted in a NPV of 0.923 (Table 4). In addition, capnometry at transfer was the individual component of the model available at the out-of-hospital setting with the best discriminative capacity (auROC: 0.679; 95 % CI: 0.547–0.802) (Fig. 2).

Table 3 – Multivariate analysis of out-of-hospital predictors of donor viability in cases of uncontrolled donation after circulatory death.

	OR	95 % CI	*P*-value
Transient return of pulse at some point during CRP	19.00	2.24–265	0.013
Mechanical chest compression (versus manual)	14.28	2.38–100	0.009
Transfer capnometry (per one-mmHg increase)	1.08	1.02–1.16	0.012
Time from the initiation of advanced CPR to hospital arrival (per one-minute increase)	1.00	0.97–1.04	0.869
Age (per one-year increase)	0.91	0.83–0.98	0.026
Death from cardiac cause	0.60	0.15–2.36	0.454
Female gender	0.32	0.02–2.72	0.340

CI: confidence interval; CPR: cardiopulmonary resuscitation; EMS: Emergency Medical Service; OR: odds ratio.

Table 4 – Diagnostic accuracy of capnometry values, warm ischemia time and multivariable model for predicting uDCD donor viability.

Parameter	Capnometry at onset of CPR, mmHg	Capnometry at midpoint, mmHg	Transfer capnometry mmHg	Capnometry trend	Warm ischemia time, minutes	Multivariable model	Viability index
Optimal cut-off value[a]	32.0	23.0	17.0	3.0	142.0		4.366
Accuracy	0.672	0.529	0.696	0.552	0.649	0.797	0.797
Sensitivity	0.423	0.538	0.923	0.500	0.423	0.846	0.846
Specificity	0.829	0.524	0.558	0.585	0.771	0.763	0.763
PPV	0.611	0.412	0.558	0.433	0.500	0.710	0.710
NPV	0.694	0.647	0.923	0.649	0.712	0.879	0.879

CPR: cardiopulmonary resuscitation; NPV: negative predictive value; PPV: positive predictive value.

[a] As assessed by the Youden's J index (J = sensitivity + specificity − 100).

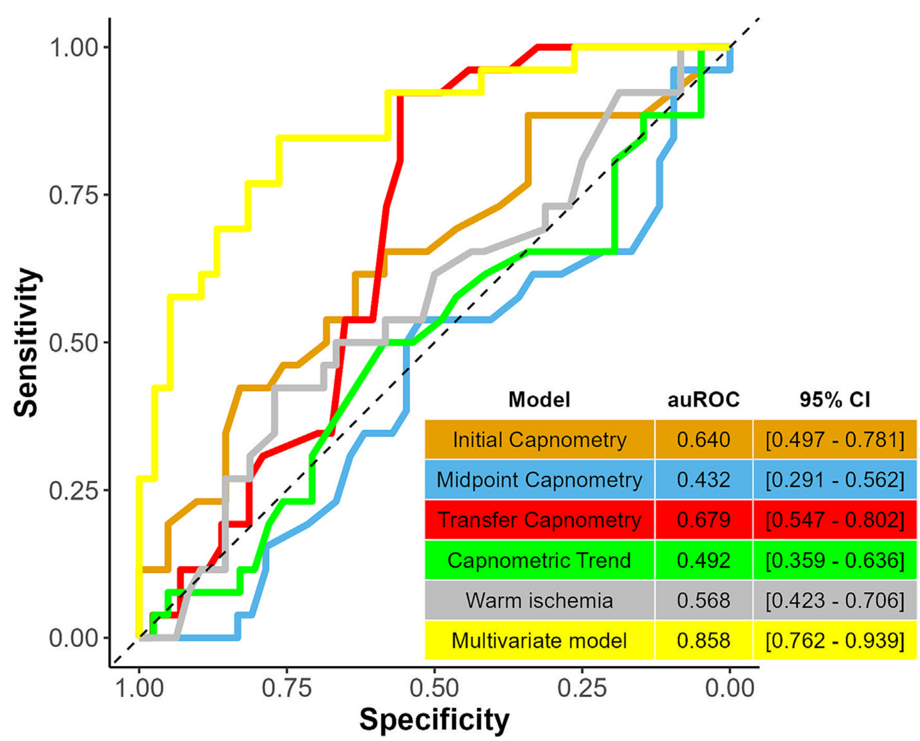

Fig. 2 – Discriminative capacity in terms of areas under receiver operating characteristic curve (auROCs) with 95 % confidence intervals (CIs) of capnometry values measured at the initiation of cardiopulmonary resuscitation (initial), at the midpoint and at arrival at the hospital (transfer), warm ischemia time and the multivariable model.

Discussion

uDCD is a complex process involving multiple factors, both in the out-of-hospital setting and upon hospital arrival, that influence the outcome of kidneys grafts. However, no studies have investigated the role of prehospital variables to predict the viability of the grafts and to differentiate valid from futile uDCD donors. We have found that younger patients that underwent mechanical chest compression, with transient return of pulse at some point during CPR and high capnometry values at arrival at the hospital (transfer capnometry) were more likely to be valid donors.

Capnometry is a non-invasive technique that can be useful in the donation process, as it allows medical professionals to estimate organ perfusion and cardiac output in potential uDCD patients and indirectly determine the metabolic status of the organs. Our group has previously reported that capnometry in donors that provided viable kidneys had an impact on the short-term graft outcome, with kidneys from donors with higher capnometry values showing faster functional recovery.[15,16]

In the present experience, the group of valid donors had higher capnometry values at the initiation of CPR than futile donors, with values approaching statistical significance. Importantly, capnometry values at time of transfer to hospital by the EMS were significantly higher in valid uDCD donors, and this association was confirmed through multivariable analysis. This is the first study describing the usefulness of this measurement for this aim, as each one-mmHg increase at arrival at hospital was associated with a 1.08-fold increased probability of obtaining a valid, non-futile kidney donor.

The optimal cut-off point was estimated for the different times at which capnometry was measured during the course of EMS care. Transfer capnometry showed an optimal cut-off point of 17 mmHg to discriminate between valid and futile donors, with 92.6 % of the valid donors being correctly predicted, and 60.5 % in the case of futile donors. This high sensitivity (the ability of a diagnostic test to correctly identify individuals who have the condition of interest, i.e., being a valid donor) makes it a valuable tool for ruling out potential uDCD donors when their capnometry values are below this cut-off value. This information may be valuable for both the EMS and transplant coordinators, allowing them to quickly identify futile donors in the context of a procedure that requires immediate decisions to be taken under pressure and mobilizes large quantities of material and human resources. In addition, the optimally selected cut-off value for the initial capnometry at the onset of CPR (32 mmHg), although not particularly sensitive, was highly specific (0.829) and provided a good PPV (0.611). Therefore, this easily available parameter would encourage to continue with the uDCD procedure.

We found statistically significant differences in donor age between valid and futile donors, both at the univariable and multivariable analyses. Each one-year decrease was associated to a 1.1-fold increase in the probability of obtaining a valid donor. This result, which is consistent with previous studies,[6,16] supports the current trend in protocols for uDCD donation to reduce to 50 years the lower limit of age to be potentially considered.

The transport of potential donors with mechanical chest compression was also more frequent in valid donors, and it was associated with a 14.2-fold higher probability of obtaining a valid donor than if CPR and the subsequent patient transport is performed on manual compression. Ours is the first study to show the advantages of mechanical cardiac compression for obtaining valid donors in uDCD. Of note, previous studies have reported conflicting results, with some of them describing advantages in terms of organ viability following manual cardiac compression[17] and others reporting better results with mechanical compression.[18] Based on our findings, we strongly recommend including mechanical compression devices in uDCD, as this approach not only increases the success rate of valid kidney donations but also improve the safety of healthcare professionals involved in the procedure.

The transient return of pulse at some point during CPR was also more common in valid donors as compared to the futile group. The recovery of spontaneous pulse during CPA leads to a period during which donor's organ perfusion and oxygenation improve, with a beneficial effect on graft viability.[19,20] Previous studies were focused on donors that were alive on arrival at the hospital and ultimately presented severe brain anoxia resulting in the declaration of brain death.[4,21–23]

There were no significant differences between the valid and futile donor groups in the time to hospital arrival. The time intervals either from CPA to the initiation of advanced CPR efforts by the EMS or from the start of advanced CPR to the arrival at the hospital and the pre-hospital warm ischemia time were very similar in both groups, with a difference of only a few minutes. This negative finding may be explained by the stringent limits for the maximum time of CPR allowed in our protocol, beyond which the uDCD procedure is interrupted.

In our analysis, the warm ischemia time showed an optimal cut-off value for predicting donor viability of 142 min. This threshold exceeds by 22 the maximum time allowed in our institutional protocols. Our result paves the way for extending the time limit currently established for the hospital arrival of the ALS, thereby increasing the pool of potential uDCD donors that may be located at a distant point or that experience transfer delays.

The main limitations of the present study were the small sample size and the absence of granular data for some donor- and process-related characteristics, such as whether there was bystander CPR prior to the EMS arrival. In addition, we lacked details on the type and parameters of ventilatory support, which may have influenced the values of capnometry. Nevertheless, we observed a clear association with graft viability despite the potential impact of this confounder. In addition, the overall missingness rate across all variables was below 5 %. Therefore, our analyses were performed on available data and no imputation methods were applied.

In conclusion, high capnometry values measured at the onset of CPR and particularly at arrival at hospital —in addition to age, use of mechanical chest compression devices and transient return of pulse— are useful to discriminate valid from futile uDCD donors. The implementation of this accessible parameter may contribute to optimize the results of the labor and resource demanding uDCD procedure.

Ethical responsibilities

All authors confirm that they have maintained confidentiality and respected the rights of the patients in the author responsibility document, publication agreement, and transfer of rights to emergencies.

CRediT authorship contribution statement

Carlos Rubio-Chacón: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Alonso Mateos-Rodríguez:** Supervision, Methodology, Investigation, Conceptualization. **Fernando Neria:** Supervision, Software, Methodology, Formal analysis. **Juan Ignacio Torres-González:** Conceptualization. **Mario Fernández-Ruiz:** Formal analysis, Data curation. **Amado Andrés:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author details

[a]Emergency Medical Service of the Community of Madrid, SUMMA 112, Madrid, Spain[b]Regional Transplant Office of the Community of Madrid, Madrid, Spain[c]School of Medicine, Universidad Francisco de Vitoria, Madrid, Spain [d]Transplant Coordination and Cell Tissue Bank, Hospital Universitario Clínico San Carlos, Madrid, Spain[e]Unit of Infectious Diseases, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (imas12), Madrid, Spain[f]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain [g]School of Medicine, Universidad Complutense, Madrid, Spain [h]Department of Nephrology, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (imas12), Madrid, Spain

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